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A Symposium: Management of Heart Failure in the 1990s: A Reassessment of the Role of Digoxin Therapy

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Introduction

Mihai Gheorghiade, MD

Cardiovascular diseases affect 1 in 4 Americans, and continue to be a major cause of death in the United States.[1] Among the cardiovascular disorders, heart failure is estimated to occur in 3–4 million individuals,[2] with approximately 400,000 cases developing each year in the United States. Hospitalization for heart failure represents the most common hospital discharge diagnosis for patients > 65 years of age.[3] It is likely that this number will increase as improved therapy for acute myocardial infarction and valvular heart disease may result in greater patient survival despite significant left ventricular dysfunction. Although available therapies are effective in reducing symptoms and improving exercise capacity, mortality among patients with heart failure remains high, with annual mortality rates of 15–50%, depending on the severity of the condition.[4]

Digitalis preparations were introduced into the treatment of cardiac abnormalities > 200 years ago. In the United States, digoxin is one of the most commonly prescribed drugs, accounting for > 12 million prescriptions in 1987. Several factors stimulated renewed interest in digoxin therapy: Randomized, double-blind, placebo-controlled trials to assess the effect of digoxin in patients with heart failure were conducted only recently. There has been a reduction in the incidence of digitalis intoxication, probably due to a better understanding of its drug interactions, as well as its use in lower doses, which has resulted in lower serum concentrations.[5] Recently, it was hypothesized that the benefits of digitalis may be related not only to its inotropic effects, but also to its neurohormonal effects.[6] Newer nondigitalis oral inotropic agents appear to increase mortality in congestive heart failure (CHF) patients[7,8]; accordingly, it is unlikely that these agents will replace digoxin in the foreseeable future.

Heart failure has a complex pathophysiology resulting from decreased cardiac contractility, plasma volume overload, and neurohormonal abnormalities; it is doubtful that one class of drugs alone will be able to control its signs and symptoms, and improve prognosis. Accordingly, a multidrug approach in the treatment of CHF must be investigated. Recent data[9,10] suggest that angiotensin-converting enzyme (ACE) inhibitors, alone or when added to therapy with digoxin and diuretics, will prolong survival in heart failure patients; however, the role of digoxin in this multidrug approach is unknown, as are expected survival times.

In addition to medical factors, the current cost and availability of cardiovascular drugs are important issues in managing CHF, particularly when an estimated 50 million Americans lack sufficient insurance coverage for major hospital and medical expenses.[11] Although clinically effective, many cardiovascular drugs can be costly. Such high costs often exclude patients in low-paying jobs and without appropriate insurance from receiving the best therapy modern medicine has to offer.[12]

Against this background, we thought it was important to reexamine the role of digitalis therapy in a multidrug approach to the treatment of heart failure. The goals of this symposium are to examine digoxin's role in clinical practice and to provide further directions for research and for developing a cost-effective and clinically beneficial therapy for heart failure patients.

Francis discusses the initial responses to myocardial injury, supporting the concept that neuroendocrine activity is an important component of the ventricular remodeling process in the progression of heart failure.

Creager suggests that abnormalities of cardio-

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pulmonary and arterial baroreceptor reflex function play a major role in altered autonomic nervous system activity in heart failure.

Mancia and his colleagues review the current knowledge in arterial baroreceptor reflex function in experimental and human CHF, suggesting that the reflex control of the cardiovascular resistance provided by a negative feedback mechanism is impaired in CHF. This impairment involves the vagal and sympathetic modulation of the heart exerted by the arterial baroreceptors.

Ferguson reviews the autonomic effects of digitalis preparations. He acknowledges that the acute administration of digitalis preparations produces a sustained sympathoinhibition and potentiates impaired arterial and cardiopulmonary baroreflex mechanisms noted in heart failure.

Tisdale and I review the hemodynamic effects of digoxin alone or in combination with other vasoactive agents in patients with heart failure, and Zarowitz and I summarize the findings of recent clinical studies of digoxin in patients with chronic heart failure and in sinus rhythm.

Yusef et al stress the importance of conducting a large randomized trial to assess the effects of digoxin on mortality in CHF.

The remainder of the symposium deals with the use of digoxin in various clinical settings.

Sarter and Marchlinski redefine the role of digoxin in patients with atrial fibrillation, suggesting that it remains the agent of choice in controlling ventricular response in patients with left ventricular dysfunction.

Podrid and colleagues acknowledge that despite the decrease in mortality, largely the result of a reduction in death due to progressive heart failure, sudden death among those patients continues to be a serious problem. They are assessing the benefits and risks of pharmacologic therapy and developing pharmacologic methods for controlling ventricular arrhythmias in patients with heart failure.

Lewis reviews the clinical use of serum digoxin concentrations. This is a particularly important topic since digoxin is one of the most commonly used drugs, and measuring serum concentrations represents a considerable medical care cost.

Kelly and Smith discuss the recognition and management of digitalis intoxication, suggesting that due to effective therapies and better understanding of drug interaction and serum concentration, the incidence and mortality of digitalis intoxication have declined markedly over the past tw decades.

Leier reviews the current status of nondigitali positive inotropic agents. He expresses disappointment in the vast effort to develop a chronically an orally administrable drug to replace or even supplement digitalis.

McCall evaluates approaches to the treatmen of asymptomatic left ventricular dysfunction, an Cody suggests ways to maximize therapy in patient with refractory heart failure. Packer concludes th symposium by evaluating long-term strategies i the management of heart failure.

It is hoped that the information presented a this symposium will help the cardiologist and th internist to reexamine critically the role of digoxi therapy in a multidrug approach to heart failure.

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Left Ventricular Hypertrophy: An Initial Response to Myocardial Injury

Gary S. Francis, MD, and Kenneth M. McDonald, MB, MRCPI

The prevailing wisdom generally has been that the failing heart hypertrophies in response to increased wall stress. The increase in myocardial mass observed in heart failure is therefore a relatively late compensatory event geared to normalize wall stress. Although this is undoubtedly true, especially for heart failure resulting from a large anterior myocardial infarction accompanied by rapid left ventricular expansion, it is possible that an important form of hypertrophy occurs much earlier as an initial response to myocardial injury. One can hypothesize that the initial response to injury is a nonspecific phenotypic alteration of the cardiac myocyte to one of growth and development. Such changes may be driven by both trophic and mechanical forces and may be important in altering the architecture of the myocardial cell and surrounding cardiac interstitium. Preliminary data from a variety of models support the concept that neuroendocrine activity is an important component in the ventricular remodeling process, and that pharmacologic interventions designed to block systemic and tissue neuroendocrine activity may prevent excessive cardiac enlargement and its ultimate consequences. Because this concept has important implications for preventive cardiology, the results of several prevention trials, including the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS), Studies of Left Ventricular Dysfunction (SOLVD), and Survival and Ventricular Enlargement (SAVE) are awaited eagerly.*

(Am J Cardiol 1992;69:3G–9G)

Cells adapt to their environment through a variety of mechanisms, including growth and development. The primary phenotype of myocardial cells is contractile; but under certain conditions, such cells can shift phenotype to one of hypertrophy while maintaining their contractile properties. The mechanisms whereby myocardial cells undergo hypertrophy are extraordinarily complex, but enough is known about the process that a coherent scheme can now be contemplated. Although not yet proven in vivo, both isolated smooth muscle vascular cells and cultured neonatal cardiac myocytes clearly hypertrophy in response to external chemical or mechanical signals that are transduced and subsequently communicate with the cell nucleus to alter phenotypic expression. All of the steps that lie between initial sensing of the signal and subsequent synthesis of new protein are not yet defined. Nevertheless, in the myocardium the general processes of growth and differentiation are beginning to be understood as adaptive responses and not merely the consequences of excessive load.

Cellular hypertrophy may be among the earliest responses to myocardial injury. In a sense, the cell adapts to a new environment by synthesizing new proteins that maintain or even enhance the contractile state. In its earliest stages, hypertrophy of the myocardium is adaptive. However, the "new" phenotype ultimately may become maladaptive.[1] Moreover, hypertrophy, even as the initial response to injury, may be the first step in the development of myocardial depression.[2] Although hypertrophy decreases the expenditure of mechanical energy by adding new sarcomeres, it causes an imbalance between energy expenditure and energy production, perhaps as a consequence of increased distance between capillaries[3] and relative underperfusion of the subendocardium.[4] Reduced subendocardial perfusion could be due to reduced coronary vasodilator reserve.[5,6] The ultimate compensation of hypertrophied myocardial cells is a reduced contractile state,[7] one of the hallmarks of congestive heart failure.

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*Editor's note: The results of these studies have been presented but have not yet been published.

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MYOCARDIAL REMODELING PROCESS

It is oversimplified to state that hypertrophy occurs in response to injury and leads to heart failure. Clearly, multiple biologic forces drive the myocardial remodeling process. For example, following acute myocardial infarction, new collagen is synthesized, "old" collagen is degraded, myofibrils slip as Starling forces increase distending pressure, and viable noninjured cells are stretched and tethered in a pattern very dissimilar to normal. Coronary blood flow reserve is impaired.[8] Muscle cell hypertrophy is a reversion to a more fetal phenotype that includes a relatively high rate of glycolytic metabolism, abundant glycogen, low myosin adenosine triphosphatase (ATPase), a preponderance of β myosin isozymes, high levels of creatine kinase-MB and lactate dehydrogenase, and a tolerance for low levels of oxygen.[9] Atrial natriuretic factor becomes expressed in ventricular tissue. These qualitative changes occur in response to external signals to the myocyte nucleus.[9,10] Eventually, the fraction of cell volume occupied by myofibrils is increased relative to mitochondrial mass[11,12]; as a result, more ATPase-consuming myofibrils must be supplied by few ATPase-generating mitochondria.[13]

Thus, one can hypothesize that the earliest stages of heart failure are characterized by myocardial injury caused by myocardial infarction in many cases, or possibly by the onset of idiopathic dilated cardiomyopathy or acute myocarditis. The adjoining remaining viable cardiac myocytes may respond to signals from injured or dying myocytes. These signals, which may be both mechanical and chemical, direct the cell nucleus to alter its phenotype. The myocardial cell is nonspecifically primed by the injury to again assume a state of growth and development, or a phenotypic change to hypertrophy. The net result is that the architecture of the myocardial cell is altered.

How does this change in shape come about? Of great interest, the cardiac myocyte alters its sarcomere structure differently in response to varying mechanical loads.[14] A pure pressure overload increases cell diameter and the number of sarcomeres in a parallel fashion (i.e., *concentric hypertrophy*),[14] whereas a volume-overloaded state increases cell diameter but also elongates cells by increasing the number of sarcomeres in series (i.e., *eccentric hypertrophy*).[14] It is possible that concentric hypertrophy is solely due to pressure load on the myocytes, whereas eccentric hypertrophy requires both alterations in loading conditions (i.e., myocyte stretch) and trophic factors, including input from the sympathetic nervous system and perhaps other peptides.[15]

Following myocardial injury caused by acute myocardial infarction, myocardial cells express both concentric and eccentric hypertrophy.[16] Eccentric hypertrophy, however, appears to be more prominent, at least experimentally.[16] Myocyte cell architecture is significantly changed in tissues adjacent to the infarct,[17] but is unchanged as distance from the infarct increases.[17,18] Loss of cardiac cells from myocardial infarction can be expected to result in greater stress on the remaining viable myocytes. The magnitude of stress is reduced by increasing cellular diameter, whereas elongation of myocytes allows enhancement of the Frank-Starling mechanism. The resultant reduction in wall stress and enhancement of end-diastolic volume serve to maintain stroke volume in the presence of reduced contractility.

Additional forces that are activated following acute myocardial infarction can potentially drive the remodeling process. Myocardial injury activates collagenase, an enzyme stored primarily outside the cells. Using radioimmunolabeling, Monfort and Perez-Tamayo[19] found collagenase on perimysial fibers around individual myocardial cells. Collagenase is produced by fibroblasts and can be activated, perhaps by oxidized glutathione to degrade collagen, given the correct circumstances.[20] It is conceivable that various forms of acute myocardial injury activate extracellular collagenase to disrupt collagen fibers, including heart failure produced by rapid ventricular pacing and doxorubicin toxicity.[21] Activation of trophic factors, including angiotensin II and aldosterone,[22] may stimulate fibroblast activity, leading to synthesis of new collagen and remodeling of the cardiac interstitium.[23] Collagen may also be produced in response to fibroblast stretch.[24] Eventually, activation of collagenase and increasing distending pressure, coupled with unusual wall stress due to loss of myocytes, leads to myocyte slippage in association with ventricular dilation and remodeling.[25] The final clinical expression is a dilated, poorly contracting heart and congestive heart failure, but the initial response to injury may be growth and development (hypertrophy) of cardiac myocytes. If the initial response to myocyte injury is growth, it may require a phenotypic change that eventually puts myocardium at risk for inefficiency and failure.

TRANSCRIPTION PROCESS

What initial signals to viable myocytes drive this phenotypic change? Clearly, altered loading conditions must play some role. Cardiac myocytes, fibroblasts (of which there are at least 4 times as many as myocytes), and leukocytes are all likely involved. Myocytes and fibroblasts are sensitive to membrane stretch, whereas leukocytes are responsive to cytokine signals. Cellular membrane stretch probably activates stretch-activated cation exchange channels, allowing calcium and sodium to enter the cell. Cyclic adenosine monophosphate (cAMP) may be activated by membrane stretch as well. These moieties—Ca^{2+}, Na^{+}, and cAMP—seem obligatory in processing certain signal responses. Calcium is required for phosphorylation of certain proteins, in some cases specific transcription regulator proteins, perhaps allowing them to translocate to the nucleus to participate in the transcription complex. RNA polymerase II, in conjunction with activated transcription factors, may then initiate the formation of nascent messenger RNA, which is translated, following a complex editing process, on ribosomal RNA in the assembly of amino acids into new protein. The new protein may take the form of additional regulatory transcription factors, growth factors, growth-factor receptors, and necessary guanine regulatory proteins (G proteins). The synthesis or activation of "chaperone" proteins may facilitate further conformational change and nuclear translocation of transcription-related cytosol proteins into the nucleus, where they are operationally involved in the transcription process.

Ultimately, new contractile proteins—in some cases less efficient contractile proteins—are synthesized and sarcomerogenesis emerges. Just how the cell assembles the new sarcomeres is unknown, but the process seems to vary, perhaps depending on certain trophic signals. In volume-overloaded ventricles, the new sarcomeres are laid down primarily in series to elongate the cell while increasing cell diameter only slightly (eccentric hypertrophy). In the case of eccentric hypertrophy, which seems the dominant response to cell injury, the sympathetic nervous system appears to play an important role.[15] Membrane-bound receptors may couple to a ligand to initiate hydrolysis of membrane phospholipids by phospholipase C to inositol 1,4,5-trisphosphate (Figure 1) and diacylglycerol. G proteins appear to govern this reaction. Inositol 1,4,5-trisphosphate in turn engages a receptor on the membrane of intracellular calcium storage vesicles to release intracellular Ca^{2+}, whereas diacylglycerol activates protein kinase C in the presence of adenosine triphosphate (ATP) to phosphorylate proteins, some of which may then interact with DNA to facilitate transcription. It is possible that phosphorylation of transcription factor proteins requires Ca^{2+} and Na^{+}, thereby drawing on the products of both stretch-activated channels and inositol 1,4,5-trisphosphate. It is certainly conceivable that norepinephrine and angiotensin II, and perhaps other growth factors, interact with sarcolemmal-bound receptors in this fashion to further drive the transcription process.

The "activated" transcription factor may require specific chaperone proteins to allow it to fold or unfold to a highly specific confirmation. The translocation of the transcription protein (transfactor) to the nucleus is probably highly regulated and may be a conformationally driven step. Once near the genome, the transcription factor may align with the DNA at a point that is both site-specific (i.e., base-sequence specific) and conformationally specific. Ultimately, RNA polymerase II in conjunction with probably several transcription factors forms a "transcription complex" to initiate transcription. mRNA is formed and "edited," or spliced, whereby exons interact with rRNA to translate the message into an amino acid sequence. A new protein is thus synthesized and transported to the cell to assume a biologic function. In cellular hypertrophy, this may include multiple possibilities, underscoring the complexity of the process.

The actual growth of the cell is highly regulated at many points. Membrane stretch and trophic factors likely work in conjunction. It is worthwhile to consider that optimizing loading conditions and inhibiting trophic factors can potentially modify phenotypic regulation and thereby prevent myocardial remodeling. Therapeutic strategies designed to prevent myocardial remodeling should combine the intricacies of molecular biology, biochemistry, and classic physiology.

TREATMENT INTERVENTIONS

Heart failure is a problem of growing magnitude in the United States. It is estimated that almost 2.5 million people suffer from this complex syndrome, accounting for approximately 240,000 deaths annually.[26] Therapy is now geared toward treating patients with established heart failure, and important new treatments have recently been initiated.[26,27] In Studies of Left Ventricular Dysfunction (SOLVD), it has been estimated that life can be prolonged about 9 months on average by adding enalapril, an angiotensin-converting enzyme (ACE) inhibitor, to established therapy with digitalis and diuretics.[26] Virtually all functional classes are benefited, but the greatest improvement in survival can be expected in patients with the lowest ejection fraction. In the Vasodilator–Heart Failure Trial II (V-HeFT II) supported by the Department of Veterans Affairs, enalapril improved survival significantly more than did hydralazine and isosorbide dinitrate.[27] In V-HeFT II, enalapril provided a proportionately greater benefit in patients with dilated cardiomyopathy than in those with underlying ischemic heart disease.[27] Although the SOLVD data indicate that enalapril resulted in no improvement in the problem of sudden death, the V-HeFT II data imply that the drug achieved a reduction in sudden and unexpected death in patients with established heart failure.[27] The reasons for this discrepancy are complex and not immediately clear. Abundantly clear, however, is that treatment with ACE inhibitors, specifically enalapril, reduces overall patient mortality, when used with conventional therapy, once the syndrome of heart failure is fully expressed.

Lessons from these and other clinical trials indicate that before we can markedly improve treatment outcome, we have to understand better the early events of myocardial injury and response to injury. If factors such as angiotensin II, collagenase, norepinephrine, and other undefined cytokines and peptides are important in driving the early, asymptomatic remodeling process, the time for pharmacologic intervention may be early. If, however, interventions are applied too early—in the acute phase of myocardial infarction, for example—the attendant reduction in coronary perfusion may offset any potential benefit.

What, then, is "early"? At this point, we simply

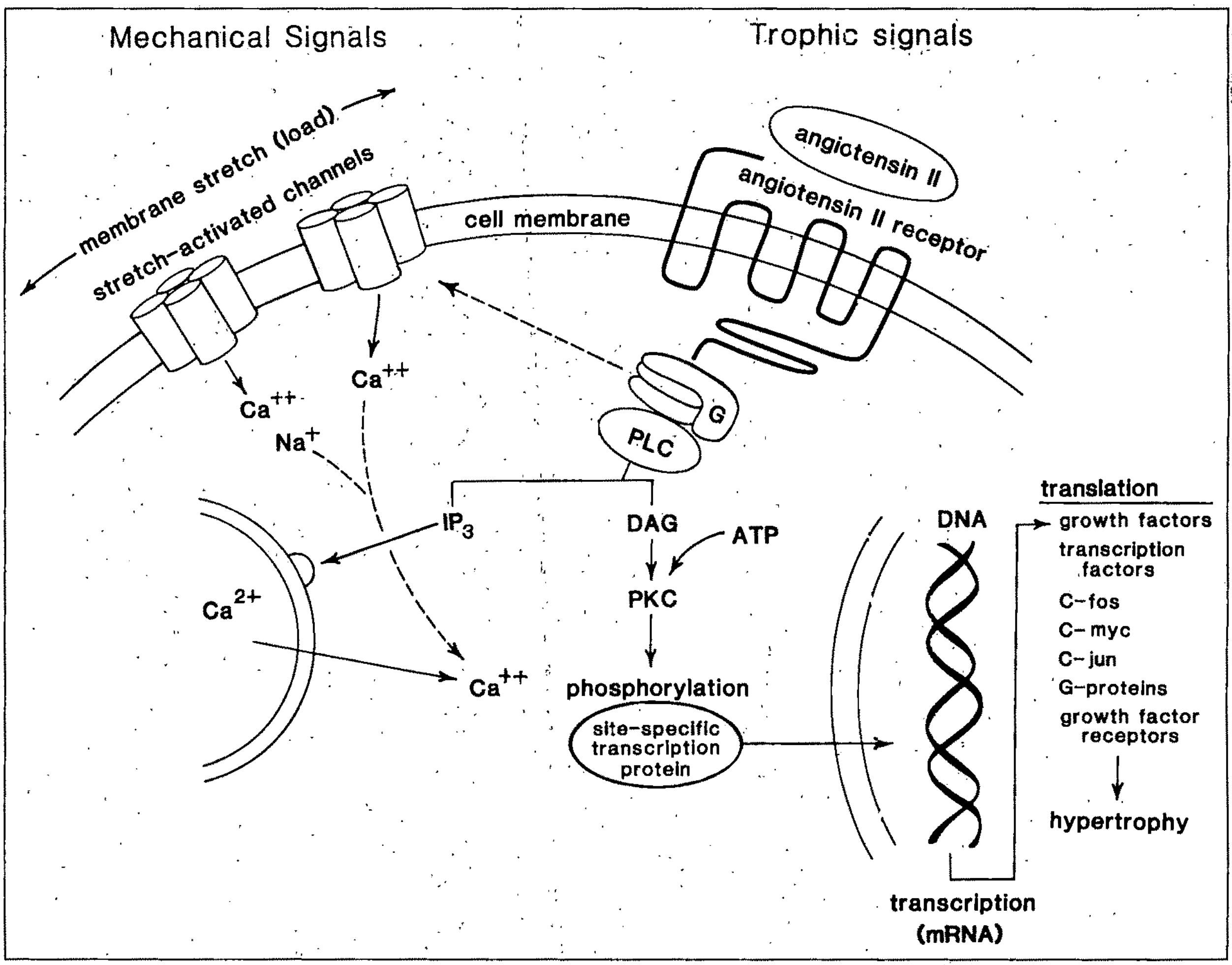

FIGURE 1. A simplified schematic proposal of how mechanical signals (membrane stretch) and neuroendocrine signals (angiotensin II) may converge to promote hypertrophy in myocardial cells. Stretch-activated channels allow for entry of essential cations into the cell, including Na^+ and Ca^{2+}. Mechanical signals (stretch or load alterations) may also signal the nucleus via tension on adhesive receptors (integrins), which are not shown. Trophic factors (e.g., angiotensin II) may bind to sarcolemmal receptors, which in turn are coupled to guanine regulatory proteins (G proteins). G proteins may enhance or inhibit cyclic adenosine monophosphate (cAMP, not shown), and possibly govern certain ion-transporter channels. Additionally, G proteins activate membrane bound phospholipase C, which in turn hydrolizes membrane phospholipids to inositol 1,4,5-trisphosphate (IP_3) and diacylglycerol (DAG) (see text). ATP = adenosine triphosphate; PKC = protein kinase C; PLC = phospholipase C.

don't know, and must await the results of the second Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS II) trial, which is addressing the use of intravenous enalaprilat in patients with acute myocardial infarction. This study, which was terminated in the spring of 1991, should be reported on soon. The Survival and Ventricular Enlargement trial, which is studying the use of captopril given at a somewhat later time following myocardial infarction, should provide critical data regarding the influence of ACE inhibitors on subsequent left ventricular (LV) function and remodeling. The prevention arm of SOLVD has now been completed; it will describe the influence of enalapril in patients with reduced LV function (ejection fraction $\leq$35%) who do not require digitalis or diuretics.

The results of these 3 studies will shed light on the concept of early intervention with ACE inhibitors in patients with myocardial injury and LV damage who are not yet symptomatic from heart failure. Experimental work with rats[28,29] and a canine model of LV damage,[30] as well as preliminary data in small numbers of patients,[31,32] appears promising. Indeed, these are extraordinary days for physicians involved in the treatment of patients with congestive heart failure, but, as always, therapeutic strategies should be driven by data and not opinions. In the long run, our patients will best be served by critical and careful scientific inquiry into the fundamental biologic processes that drive the disease.

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DISCUSSION

Dr. Packer: The concept of hypertrophy preceding dilation is controversial. If you activate the renin–angiotensin system, vasoconstriction will take place very quickly. If vasoconstriction is the major cause of ventricular dilation, then the latter should soon follow. Accordingly, this would cause ventricular growth that would be time-dependent. So, based on the concept that vasoconstriction is fast and ventricular growth is slow, you would expect dilation to occur first and left ventricular hypertrophy second. However, that is not what is found.

Dr. Francis: By an increase in volume I do not mean an expansion of infarct, which occurs very quickly with large anterior myocardial infarctions (MIs). There, you clearly get a big increase in ventricular volume that precedes the hypertrophy. In such cases, the heart will hypertrophy in response to this increase in volume, and that is probably useful, because it will maintain wall stress.

I believe there is a larger group of patients who have more intermediate-size MIs. These MIs do not expand but, rather, stimulate hypertrophy as the initial response. We know that the time course of "hypertrophy" in these patients is very quick, within hours, at least as measured by protooncogene expression.

My sense is that circulatory control is quite separate from the hypertrophic response. Circulatory control probably evolved 600 million years ago, whereas hypertrophy—and how the cell responds to injury—is a much more primitive response. Molecular evolutionists tell us it took probably 1 billion years for the cell to evolve from single-cell to multicellular organisms. During that time, I suspect, certain peptides and stretch-activated channels involved with hypertrophy evolved as protective mechanisms.

Dr. Gheorghiade: How do you know which response is compensatory and which is damaging?

Dr. Francis: I think these systems are designed to aid the cell and, ultimately, the organ and the organism. Hypertrophy is basically a compensatory response. Maintenance of wall stress is very important. I believe, however, that both hypertrophy and dilation ultimately may become excessive responses, in that the mechanisms leading to each do not shut off. If we could intervene at the right time and block those growth forces, which are presumably being driven by peptides and neuroendocrine systems, perhaps we could halt these compensatory responses before they become detrimental.

Dr. Yusuf: How do you measure compensation?

Dr. Francis: It is a conceptual definition; it is not something we can measure in the laboratory. There are, however, cases in which hypertrophy occurs without a need; it occurs without a huge increase in volume—it may even precede the increase in volume.

Dr. Leier: Our inability to test these concepts scientifically makes it very difficult to determine whether hypertrophy and dilation serve in a compensatory or detrimental role. Except in a few isolated cases, such as aortic stenosis, I am inclined to believe that hypertrophy and, to a certain degree, dilation are compensatory, but I am not totally certain.

Dr. Francis: We know hearts remodel in response to MI, and this is not good. In fact, the remodeling process involves ventricular dilation and hypertrophy. There are drugs that appear to inhibit this process—angiotensin-converting enzyme (ACE) inhibitors, for example, may prevent remodeling (they certainly do in the experimental laboratory).

But how do they do this? Do they alter loading conditions by blocking systemic neuroendocrine activation? Or do they block the tissue response to injury? Probably both mechanisms are operative, but we need to think about this, I believe, and develop drugs that will be more selective. For example, we now have drugs that block protein kinase C activity. When we learn more about what goes on within the cell, we might be able to target specific intracellular pathways to block the "bad" hypertrophy and allow the "good" hypertrophy to ensue. I think that is the direction future research should be headed.

Dr. Kelly: The renin–angiotensin system within the heart has been like the grail—sought after but not found. No one doubts its existence. I think angiotensinogen is either taken from the bloodstream or perhaps produced locally. Renin is probably the rate-limiting enzyme, although which cells produce it and other components of this system within the ventricular wall of the heart is unclear.

There is controversy about whether ACE is the appropriate converting enzyme—whether there is not another converting enzyme within the interstitium. Dr. Francis, what are your thoughts on this?

Dr. Francis: Some noted experts are really very skeptical about the existence of an intracellular renin–angiotensin system, particularly within the heart.

I believe there is renin–angiotensin activity within the cell. You can measure the message for both the substrate and the converting enzyme. That does not mean, necessarily, that the protein is being synthesized and is biologically functional, but I suspect we will be able to clarify this when we have the technology. I think Helmut Drexler's as-yet unpublished observation that, indeed, an increment exists in the mRNA for the substrate, angiotensinogen, in homogenized rat myocardium following MI certainly supports the notion that there is an intracellular system. But I do not think any direct data taken from isolated myocytes or other cardiac cells indicate the presence of an intracellular renin–angiotensin system.

Dr. Yusuf: In SOLVD there is a substudy on left ventricular function and mass. During treatment, left ventricular volumes were smaller in the enalapril group compared with the placebo group. At the end of the study, all patients were withdrawn from blinded treatment for 2 weeks. In that period, ventricular volumes reverted partly toward baseline levels in the enalapril group. So with volume changes, part of the benefit is a continuing acute hemodynamic effect as opposed to an underlying remodeling effect. Obviously, this study cannot tell us about hypertrophy or change in shape.

Dr. Francis: However, the implication is that enalapril holds the volume expansion in check. I think that is a very important observation.

Baroreceptor Reflex Function in Congestive Heart Failure

Mark A. Creager, MD

Congestive heart failure is characterized by decreased parasympathetic and increased sympathetic nervous system activity. Impairment of baroreceptor reflex function may be relevant to this altered neural profile. The effect of cardiopulmonary and arterial baroreceptor stimulation on corresponding afferent neural activity is reduced in experimental models of heart failure. In addition, the heart rate and blood pressure responses to perturbations in arterial and carotid sinus pressure are less in animals with heart failure than in control animals. Comparable observations have been made in humans. Unloading cardiopulmonary baroreceptors with lower-body negative pressure causes less forearm vasoconstriction in patients with heart failure than in healthy subjects. The chronotropic response to changes in arterial and carotid sinus pressure induced by drug infusions or by use of a neck chamber is attenuated in heart failure. These data suggest that abnormalities in cardiopulmonary and arterial baroreceptor reflex function contribute importantly to altered autonomic nervous system activity in heart failure.

(Am J Cardiol 1992;69:10G–16G)

Sympathetic nervous system activity is increased and parasympathetic nervous system activity is decreased in most patients with congestive heart failure (CHF).[1–5] Normally, autonomic balance is regulated by afferent input from multiple peripheral receptors, including baroreceptors in the heart, lungs, and great vessels, chemoreceptors in the carotid bodies, metaboreceptors in skeletal muscle and sensory receptors in skin, a variety of visceral receptors, and from signals originating in the central nervous system. Of these, the baroreceptors are the principal modulators of sympathetic and parasympathetic activity during changes in intravascular volume or pressure. Mechanoreceptors in the heart and pulmonary vasculature (cardiopulmonary baroreceptors) and in the aortic arch and carotid sinus (arterial baroreceptors) respond to stretch by relaying afferent neural signals via branches of the vagus and glossopharyngeal nerves to the central nervous system. These signals inhibit sympathetic and augment parasympathetic efferent activity. In states of plasma volume depletion or hypotension, decreased receptor stretch reduces the afferent stimuli, thereby decreasing parasympathetic activity and increasing sympathetic activity. It is somewhat ironic that the balance of sympathetic and parasympathetic activity in heart failure, a disorder characterized by plasma volume excess, is similar to that observed during plasma volume depletion. The similarities compel a careful examination of cardiopulmonary and arterial baroreceptor reflex function in heart failure.

CARDIOPULMONARY BAROREFLEXES IN EXPERIMENTAL HEART FAILURE

Several experimental models of heart failure have been used to examine cardiopulmonary baroreceptor reflex activity. Greenberg et al[6] measured atrial receptor activity during progressive increases in atrial pressure and stretch induced by a dextran infusion in dogs subjected to tricuspid avulsion and pulmonary artery stenosis. Atrial firing rate was less in dogs with heart failure than in

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control dogs. Zucker et al[7] measured left atrial receptor activity during increases in left atrial pressure in dogs with high-output heart failure caused by creation of an aortocaval fistula. These investigators also found that atrial receptor sensitivity was decreased in dogs with heart failure compared with control dogs. They attributed these abnormalities to both decreased atrial compliance and abnormalities in atrial receptor morphology. Of note, atrial receptor sensitivity returned to normal approximately 8 weeks after the aortocaval fistula was ligated and signs of heart failure had abated.[8] These observations suggest that cardiac baroreceptor function is abnormal in animal models of heart failure and implicate at least one mechanism through which afferent modulation of sympathetic and parasympathetic efferent activity may be altered.

ARTERIAL BAROREFLEX FUNCTION IN EXPERIMENTAL HEART FAILURE

There have been many more investigations of arterial than of cardiopulmonary baroreceptor reflex function in experimental models of heart failure. A variety of experimental models have been employed, and both aortic and carotid sinus baroreceptors and afferent as well as efferent aspects of the baroreflex arc have been investigated. Several studies examined arterial baroreceptor reflex function in dogs with low-output failure induced by tricuspid regurgitation and pulmonic stenosis. Higgins et al[9] were the first to report that the bradycardic response to increases in blood pressure caused by an infusion of phenylephrine was reduced in this model of heart failure. They also found that increases in heart rate, blood pressure, and mesenteric and renal vascular resistances during bilateral carotid artery occlusion were attenuated in dogs with heart failure. In this same model, White[10] found that the bradycardic and vasodepressor responses to increases in carotid sinus pressure were blunted compared with control dogs. He attributed a portion of these observations to impaired end-organ function, since the heart rate responses to both acetylcholine and vagal stimulation were reduced in dogs with heart failure. Niebauer and Zucker[11] examined arterial baroreceptor function in dogs with high-output heart failure caused by creation of an aortocaval fistula. They measured carotid sinus nerve activity during stepwise and continuous (ramped) increases in carotid sinus pressure. Carotid sinus baroreceptor gain was decreased in dogs with heart failure during both stepwise and slow continuous increases in carotid sinus pressure.

More recently, investigators have examined arterial baroreceptor reflex function in a canine model of heart failure induced by rapid ventricular pacing. In this model, the hemodynamic and neurohumoral changes that occur are similar to those found in humans with heart failure. Dibner-Dunlap and Thames[12] measured aortic and renal nerve activity during changes in blood pressure induced by phenylephrine and nitroglycerin infusions in anesthetized, ventricular-paced dogs. They reported decreased gain of aortic nerve activity during changes in blood pressure in dogs with heart failure, implicating an abnormality in arterial baroreceptor function (Figure 1).[12] They found, however, that gain reflecting baroreceptor input and renal sympathetic efferent activity was not reduced in dogs with heart failure, and they suggested that central mechanisms may be pertinent in preserving sympathetic efferent activity in this model.

Wang et al[13–15] reported on a series of experiments examining carotid sinus baroreceptor activity in ventricular-paced dogs. They found that incremental carotid sinus pressure increased baroreceptor activity less in dogs with heart failure than in control dogs (Figure 2).[13] They also noted that postexcitatory depression of carotid baroreceptors is prolonged in dogs with heart failure,[14] and that changes in carotid sinus baroreceptor activity did not always parallel renal sympathetic efferent activity in this model.[15] During increases in carotid sinus pressure, changes in renal sympathetic nerve activity were similar in control and heart failure dogs. In addition, during electrical stimulation of the carotid sinus nerve, decreases in renal sympathetic nerve activity were similar in control and heart failure dogs. This observation is similar to the one made by Dibner-Dunlap and Thames[12] regarding arterial baroreceptor function, as discussed above. It raises the possibility that central mechanisms may compensate, in part, for abnormalities in afferent input.

Alternatively, abnormalities in arterial baroreceptor function may be more pertinent to heart rate control than to regulation of regional vascular resistance. Wilson et al[16] examined this possibility in anesthetized ventricular-paced dogs during infusions of phenylephrine and nitroglycerin. There was an impaired heart rate response to changes in blood pressure; however, arterial baroreflex control of hind-limb vascular resistance was preserved in dogs with heart failure.

Taken together, these experiments confirm the existence of abnormalities in both carotid sinus and aortic baroreceptor function in heart failure. Baroreceptor activity is generally less in dogs with heart failure than in healthy dogs during comparable changes in blood pressure. The precise mechanism or mechanisms that cause abnormalities in arterial baroreceptor dysfunction have not yet been defined, although several have been suggested. Wang and colleagues[13,14] have speculated that excessive sodium, potassium–adenosine triphosphatase (Na^+,K^+-ATPase) activity may impair arterial baroreceptor function. They found that ouabain increased carotid sinus baroreceptor sensitivity and reduced the duration of postexcitatory depression in dogs with heart failure. They could not attribute the abnormalities in baroreceptor sensitivity to decreased arterial compliance, since carotid sinus distensibility was similar both in control dogs and dogs with heart failure. Having found naloxone improved baroreceptor sensitivity in dogs with heart failure, Sakamoto and Liang[17] suggested that increased β-endorphin levels may impair arterial baroreceptor sensitivity in heart failure, probably by their effect on central opiate receptors.

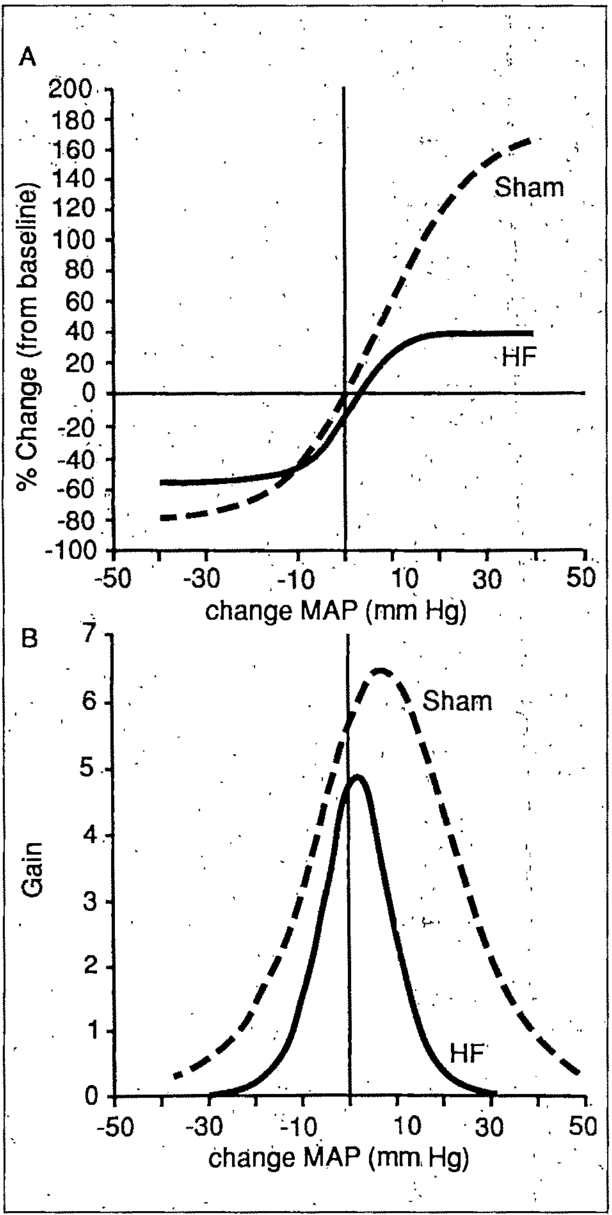

FIGURE 1. The effect of increases in mean arterial pressure (MAP) caused by phenylephrine infusion on aortic nerve activity in healthy dogs (SHAM) and in dogs with congestive heart failure (HF) secondary to rapid ventricular pacing (*A*). There is decreased gain of aortic nerve activity in the dogs with heart failure (*B*). (Reproduced with permission from The American Heart Association.[12])

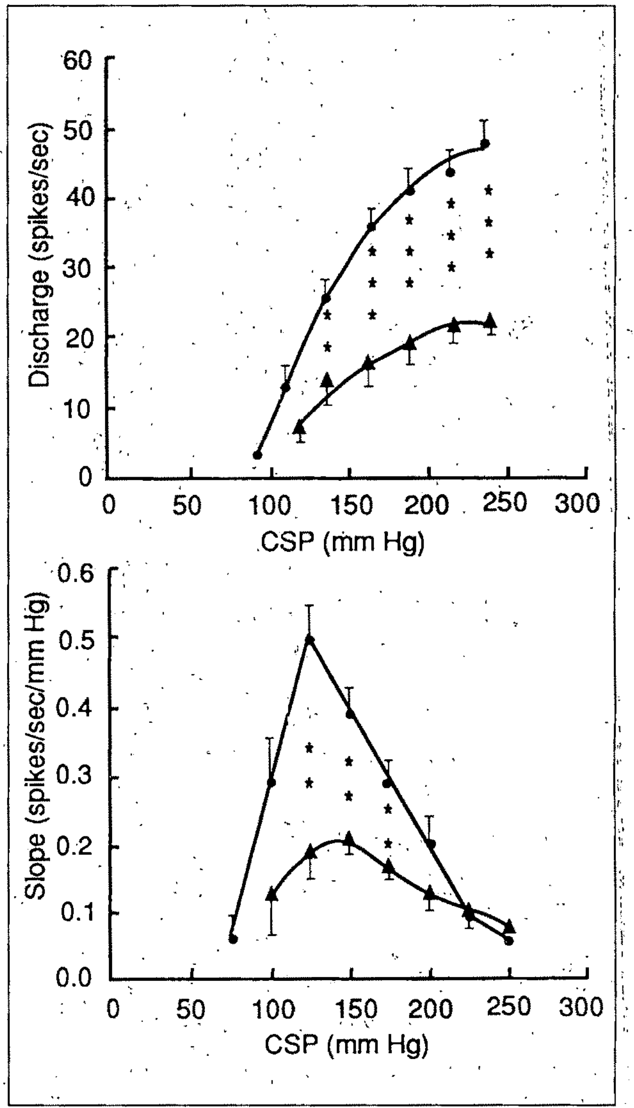

FIGURE 2. The effect of incremental carotid sinus pressure (CSP) on carotid sinus nerve activity in healthy dogs (●) and in dogs with heart failure (▲) induced by rapid ventricular pacing (*top*). Carotid sinus sensitivity is decreased in dogs with heart failure (*bottom*). (Reproduced with permission from The American Heart Association.[13])

BAROREFLEX FUNCTION IN HUMANS WITH HEART FAILURE

An abnormal chronotropic response to upright tilt in humans with heart failure was first reported by Howard and Leathart in 1951.[18] These findings have been confirmed and extended many times since then. During upright tilt, heart rate, systemic vascular resistance, and plasma norepinephrine concentration increase less in patients with heart failure than in normal subjects.[19–23] It is impossible to distinguish abnormalities in cardiopulmonary from arterial baroreceptor reflexes, since upright tilt unloads both sets of receptors. To examine cardiopulmonary baroreceptor reflex function in patients with CHF, several groups of investigators have employed lower-body negative pressure. Patients are enclosed in a lower-body negative-pressure chamber sealed at the iliac crest and studied in the supine position. Low levels of lower-body negative pressure reduce venous return and lower cardiac filling pressure without altering arterial pressure. Thus, this maneuver enables characterization of the reflex responses to cardiopulmonary baroreceptor unloading. Low levels of lower-body negative pressure elicit forearm vasoconstriction in normal subjects but not in patients with CHF (Figure 3).[24–26] Consistent with observations in animals, these findings suggest that cardiopulmonary baroreceptor reflex function is abnormal in humans with CHF.

Many studies in humans have measured the chronotropic response to increases in blood pressure induced by phenylephrine and decreases in blood pressure caused by nitroglycerin or nitroprusside. Such infusions are often used to examine arterial baroreceptor reflex function, but one cannot discount the influence of these vasoactive drugs on cardiac filling pressures. Nonetheless, studies have consistently reported impaired baroreceptor–heart rate reflex sensitivity in patients with CHF.[27–29] Reduced sensitivity may result from abnormalities in the arterial baroreceptors and their afferent neurons, altered central mechanisms, impaired transmission of sympathetic and parasympathetic efferent neurons, or reduced sinus node responsiveness. Indeed, Porter et al[5] reported that reduced parasympathetic efferent activity is caused, in part, by abnormalities within the central nervous system. Low doses of atropine, which increases parasympathetic activity by stimulating central vagal neurons, decreased heart rate in normal subjects but not in patients with heart failure. High parasympatholytic doses of atropine increased heart rate to a lesser extent in heart failure patients than in healthy subjects. It is not known whether sinus node responsiveness to cholinergic stimuli is impaired in

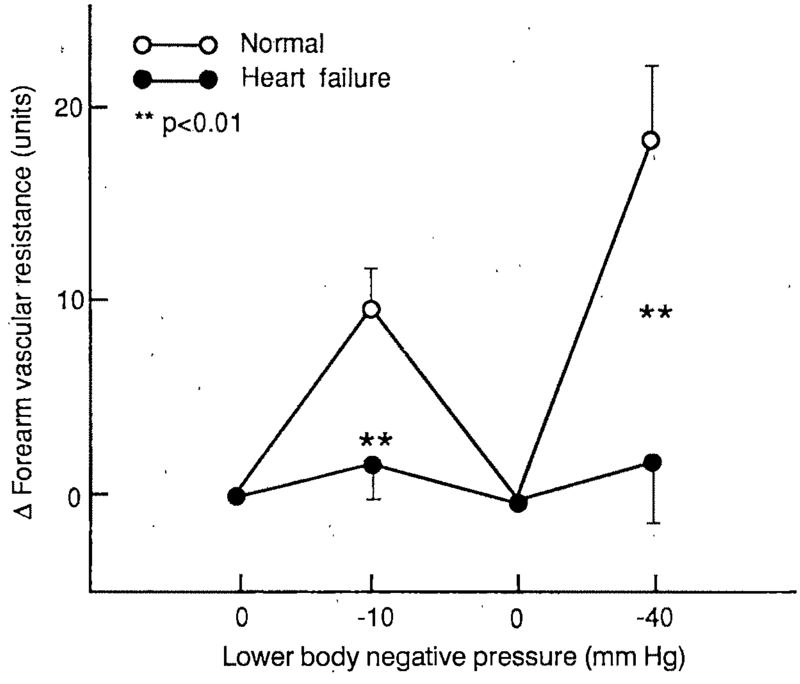

FIGURE 3. The effect of lower-body negative pressure on forearm vasoconstriction in normal subjects and in patients with congestive heart failure. Low levels of lower-body negative pressure (− 10 mm Hg) unload cardiopulmonary baroreceptors, whereas high levels (− 40 mm Hg) unload both cardiopulmonary and arterial baroreceptors. Forearm vasoconstriction occurs during lower-body negative pressure in normal subjects but not in patients with congestive heart failure.

patients with heart failure as it is in experimental models.[10] Colucci et al[30] found that the chronotropic effect of isoproterenol is reduced in individuals with heart failure.

It is much more difficult to confine investigations to specific baroreceptors in humans than it is in animals. Several groups of investigators have used a neck chamber to study carotid sinus baroreceptor reflex function. Decreases in neck chamber pressure increase carotid artery transmural pressure and stimulate carotid sinus baroreceptors. Conversely, increases in neck chamber pressure decrease carotid artery transmural pressure and unload carotid sinus baroreceptors. Sopher et al[31] used a ramped neck pressure–suction sequence to unload and stimulate carotid sinus baroreceptors, measuring heart rate at each step to calculate arterial baroreceptor reflex sensitivity. Arterial baroreceptor–heart rate reflex sensitivity was less in patients with heart failure than in normal subjects (Figure 4).[32] Thus, as observed in animals, carotid sinus baroreceptor–reflex function is abnormal in humans, at least in terms of regulating heart rate.

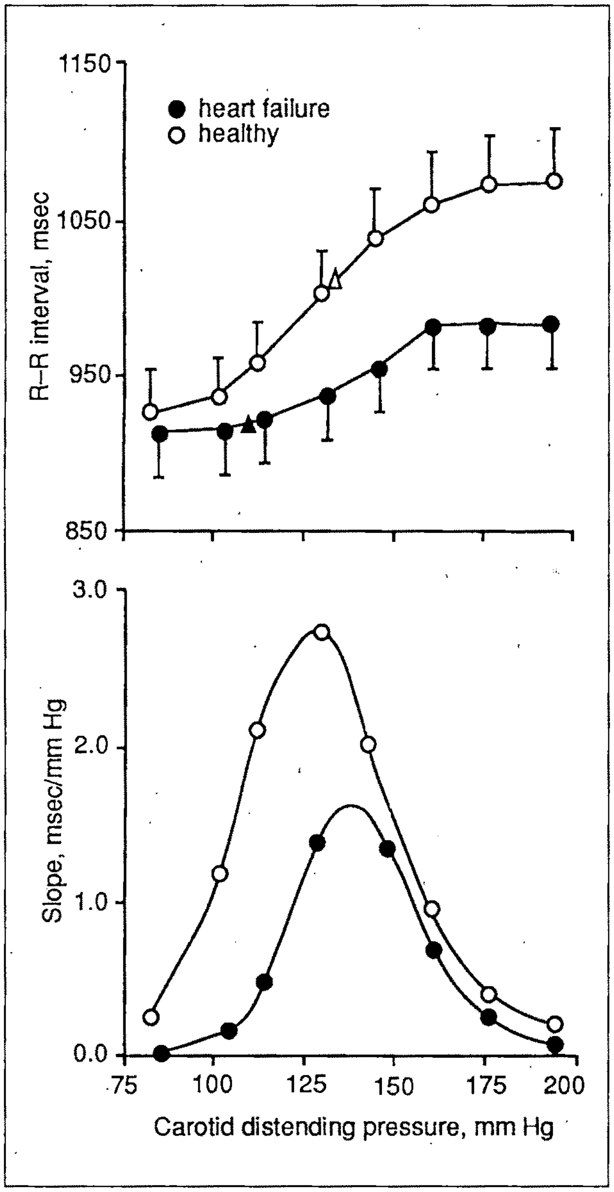

FIGURE 4. The heart rate response to perturbations in carotid sinus pressure (*top*). A ramped neck pressure–suction sequence is used to unload and stimulate carotid sinus baroreceptors (illustrated as transmural carotid pressure on the x axis). The sensitivity of the carotid sinus baroreceptor–heart rate reflex is less in patients with heart failure than in normal subjects (*bottom*). (Reproduced with permission from The American Physiological Society.[31])

Creager and Gallagher[32] used a similar experimental design, but examined the blood pressure responses to perturbations and carotid sinus pressure. The blood pressure response to carotid sinus unloading was attenuated in patients with CHF, whereas responses to carotid sinus stimulation were similar in healthy and heart failure subjects. These findings suggest that in patients with CHF, the operational point of carotid sinus baroreceptors is close to threshold, enabling them to respond appropriately to stimuli but not to further unloading. Alternatively, central mechanisms may compensate for abnormal afferent neural input, as has been suggested in experimental models of heart failure.[12,15] It is less likely that end-organ responsiveness accounts for the reduced blood pressure response to carotid sinus unloading. Intra-arterial phenylephrine increases forearm vasoconstriction comparably in healthy subjects and patients with heart failure.[26]

CONCLUSION

Baroreceptor reflex abnormalities are evident in experimental models of heart failure and in humans with CHF. Reduced afferent input from these receptors likely contributes to the excessive sympathetic and reduced parasympathetic activity that are characteristic of CHF. Thus, there may be a rational explanation for the similar neural profile observed in volume-depleted states and in heart failure. In the former, baroreceptors function normally in response to reduced volume and pressure. In the latter, baroreceptor reflex function is impaired and fails to augment parasympathetic or adequately throttle sympathetic nervous system activity.

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DISCUSSION

Dr. Gheorghiade: In patients with asymptomatic left ventricular (LV) dysfunction, are there abnormalities in cardiopulmonary baroreceptor sensitivity?

Dr. Creager: I am unaware of any studies that have examined baroreceptor function in asymptomatic individuals with LV dysfunction.

Dr. Gheorghiade: Should we assume that such abnormalities exist, since there is an increase in serum norepinephrine concentration and plasma renin activity (PRA) in these patients? [1]

Dr. Creager: We can raise that as a reasonable hypothesis.

Dr. Gheorghiade: Does a decrease in cardiopulmonary baroreceptor sensitivity in congestive heart failure develop gradually, or all at once?

Dr. Creager: It is probably a gradual phenomenon, analogous to hypertension. If you acutely raise blood pressure in hypertensive patients, the rate at which you affect baroreceptors is going to be proportional to the rapidity as well as the severity of the blood pressure increase.

Dr. Cody: I was struck by the article that Gary Francis published regarding neurohormonal data in the Studies of Left Ventricular Dysfunction (SOLVD).[1] I think the fact that the increase in PRA in asymptomatic patients was influenced by diuretics is not a small observation. Five years ago that would have been nothing short of revolutionary. Being able to demonstrate this in such a large population is very important.

The vasopressin issue is also very important. We published some data about 6 years ago demonstrating that if you separate the platelet-rich from the platelet-free components of plasma, you find very high concentrations of arginine vasopressin (AVP) in platelets. There is probably a very dynamic kinetic relationship between plasma and platelet AVP.

It is not surprising that catecholamines release a large number of substances from platelets, not the least of which could be AVP. It is well documented that norepinephrine levels are increased even in very early asymptomatic stages of heart failure. In addition to the well-described influence of catecholamines on renin release, catecholamines may also influence AVP release from platelets.

Dr. Yusuf: Once the patients receiving diuretics were removed from the SOLVD database, however, the investigators found no real increase in PRA but small increases in plasma norepinephrine and AVP. We know plasma norepinephrine and AVP should affect PRA release. So there is a dissociation in the so-called asymptomatic group that intrigues me.

Dr. Creager: Sympathetic efferent activity may stimulate renal release, whereas vasopressin may attenuate it. On balance, early in heart failure, there may be no net change in PRA. In more severe forms of heart failure, diuretics lower renal perfusion pressure and increase proximal resorption of sodium, contributing to renin release.

Dr. Yusuf: I think 15 or so patients were not taking diuretics and had a normal PRA. This is at variance with data from India published in *Circulation* in which patients with severe heart failure who were not receiving diuretics had elevated PRA. So perhaps in mild heart failure PRA is still normal, which leads me to speculate that the beneficial effects of angiotensin-converting enzyme (ACE) inhibitors observed in severe heart failure (and perhaps moderate heart failure) in some ways antagonize the harmful effects of diuretics.

Dr. Gheorghiade: Should we try to attenuate the neuroendocrine abnormalities noted in patients with asymptomatic LV dysfunction?[2]

Dr. Creager: I think most of us would agree that neurohormonal abnormalities are markers of prognosis. As more patients and neurohormones are evaluated, the likelihood of finding correlations increases. Norepinephrine has been known to be a marker for prognosis for a while. Now enough data are available to show that plasma renin activity is a marker.

Dr. Yusuf: In 900 people with mild-to-moderate (predominantly class II) heart failure, we showed that plasma norepinephrine and PRA are predictors of mortality and morbidity, morbidity being hospitalization for heart failure.

Dr. Creager: That does not surprise me. But it would be speculation to state that interventions that improve prognosis are doing so by correcting these neurohormonal abnormalities as opposed to direct effects on heart and blood level function. ACE inhibitors, we all agree, improve prognosis, but it remains to be determined whether they do it by interfering with the systemic renin–angiotensin system, the tissue renin–angiotensin system or by effecting morphologic changes in the left ventricle or in the blood vessel.

Dr. Leier: Can you speculate as to how baroreceptor dysfunction evolves?

Dr. Creager: Injury to the left ventricle may affect not only myocytes, but also the other structures in the heart, including baroreceptors. Infarction, inflammation, and infiltrative disorders could therefore affect baroreceptor function as well. Excessive stretch caused by high cardiac filling pressures may contribute to baroreceptor dysfunction, particularly in the atria and the pulmonary vasculature. Also, changes in the ionic milieu may be relevant to baroreceptor dysfunction.

Dr. Leier: Perhaps a reset phenomenon?

Dr. Creager: It has been shown that restoration of normal or cardiac filling pressures improves baroreceptor function. Following ACE inhibition, the vasoconstrictive response to upright tilt improves. Other forms of heart failure treatment—including digitalis, glycosides, and cardiac transplantation—improve baroreceptor reflex function.

There are at least 3 proposed mechanisms of baroreceptor dysfunction in the arterial tree in patients with heart failure. One is compliance. When the larger vessels are stiff, they do not distend appropriately with changes in pressure. We and others have shown that compliance is decreased in the carotid arteries.

A leading theory cites abnormalities of the Na^+,K^+-ATPase pump. Ouabain has been shown to improve carotid sinus baroreceptor function in a dog model of heart failure.

A third, very intriguing, theory is based on endothelial contributions to baroreceptor function. Prostaglandin I_2 (prostacyclin) sensitizes baroreceptors, whereas use of indomethacin decreases baroreceptor function. It is not known whether prostacyclin or other endothelial-derived vasoactive modulators influence baroreceptor function in CHF.

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Reflex Cardiovascular Control in Congestive Heart Failure

Giuseppe Mancia, MD, Gino Seravalle, MD, Cristina Giannattasio, MD, Mario Bossi, MD,
Laura Preti, MD, Bianca M. Cattaneo, MD, and Guido Grassi, MD

This article reviews evidence that the reflex control of the cardiovascular system provided by negative feedback mechanisms is impaired in congestive heart failure (CHF). The impairment involves vagal and sympathetic modulation of the heart exerted by arterial baroreceptors. It also affects baroreceptor control of blood pressure and peripheral vascular resistance, as well as the cardiopulmonary receptor's ability to modulate sympathetic activity. The degree of such impairment is most marked in severe CHF but is also apparent, to a minor degree, in mild heart failure. Reflex impairment is due to a reduction in the receptor signal, but other factors under investigation are probably also involved. Digoxin and other pharmacologic treatments of CHF improve reflex function, thereby facilitating a reduction in the elevated sympathetic activity and a stepping up of the reduced vagal activity typical of CHF. This may be relevant to a patient's prognosis.

(Am J Cardiol 1992;69:17G–23G)

Congestive heart failure (CHF) is characterized by reduced vagal tone and increased sympathetic tone, which are partly responsible for the tachycardia and systemic vasoconstriction found in this condition.[1,2] The mechanisms responsible for these autonomic changes are not entirely clear. Studies in animals and humans, however, indicate that in CHF the arterial baroreflex is impaired,[3] which suggests that a reduction in reflex sympathetic inhibition and vagal stimulation is involved.

This article briefly reviews current knowledge of arterial baroreflex function in experimental and human CHF, including the effect of this disease on another major reflex, i.e., the reflex originating from volume receptors in the cardiopulmonary region.[4]

BARORECEPTOR–HEART RATE REFLEX

Mean arterial pressure, pulse pressure, and arterial *dP/dt* (ratio of change of arterial pressure to change in time) are reduced in CHF, which means that the above-mentioned increase in sympathetic drive and reduction in vagal tone might be simply explained by a reduced baroreceptor stimulus. CHF, however, is also accompanied by a marked reduction in the sensitivity of the baroreceptor–heart rate reflex.[5] This is exemplified in Figure 1,[5] which shows how bradycardia is induced by stimulating the baroreceptors via an increase in systolic blood pressure (BP) obtained with an intravenous bolus of phenylephrine. Compared with 23 control subjects, the slope of the bradycardic response was markedly diminished in 22 patients with CHF.[5] The tachycardia induced by unloading baroreceptors via a reduction in BP obtained through an intravenous vasodilator was also reduced in CHF,[6] demonstrating that impairment involves the whole stimulus–response curve of the reflex.

Other questions concerning the baroreceptor–heart rate reflex in CHF are whether impairment: (1) depends to some extent on the etiology of CHF;

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(2) is proportional to its severity; or (3) is mediated by an impairment of vagal or sympathetic cardiac modulation. The first question cannot be answered because, although heart failure with different etiologies (e.g., rheumatic fever, congenital heart disease, coronary heart disease) is associated with reduced sensitivity of the baroreceptor–heart rate reflex,[5-8] no study has ever investigated this issue in a comparative fashion. Also, no comparative study has ever examined the effect of CHF of varied severity on the baroreflex, an issue that is made particularly complex by the discrepancy between classifications of heart failure severity. In 10 patients with New York Heart Association (NYHA) class II congestive cardiomyopathy, for example, we found that the tachycardic response to an intravenous infusion of nitroprusside was normal but that the bradycardic response to an intravenous infusion of phenylephrine was strikingly reduced. In all patients, however, fractional left ventricular shortening was so obviously compromised as to challenge the conclusion that impairment of the baroreceptor–heart rate reflex extends to cases of mild CHF (unpublished data) (Figure 2).

The third question, on the other hand, has been answered by studies that have examined the baroreceptor–heart rate reflex of patients with CHF before and after administration of atropine and propranolol.[4-6] It has been clearly shown that baroreceptor control of both vagal and cardiac sympathetic drive is depressed and, thus, that CHF modulation affects the whole reflex autonomic control of the heart.

BARORECEPTOR CONTROL OF SYSTEMIC CIRCULATION

In several physiologic and pathophysiologic conditions (exercise, aging, hypertension, etc.), baroreceptor control of heart rate is impaired to a much

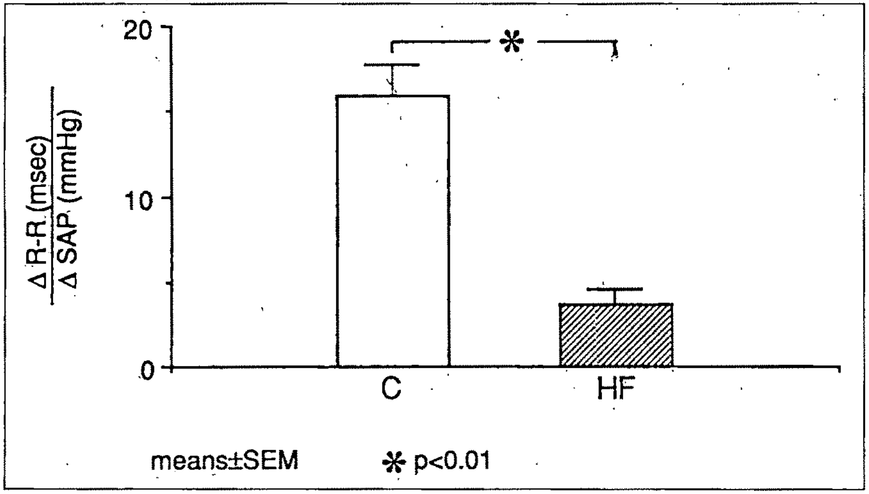
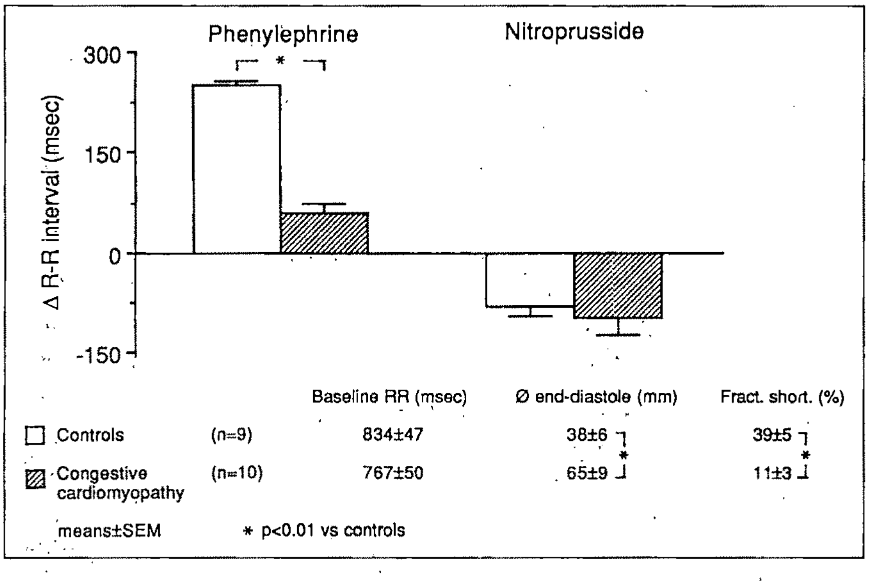


FIGURE 1. Lengthening in R-R interval induced by increasing systolic arterial pressure (SAP) with an intravenous bolus of phenylephrine in healthy control subjects (C) and in age-matched patients with heart failure (HF). (Modified from *N Engl J Med*.[5])



		Baseline RR (msec)	Ø end-diastole (mm)	Fract. short. (%)
☐ Controls	(n=9)	834±47	38±6 *	39±5 *
▨ Congestive cardiomyopathy	(n=10)	767±50	65±9	11±3

means±SEM * p<0.01 vs controls

FIGURE 2. Increases and reduction in R-R interval induced, respectively, by phenylephrine and nitroprusside intravenous infusions in healthy control subjects and in age-matched patients with congestive cardiomyopathy. Baseline R-R intervals and echocardiographic values for end-diastolic diameters and fractional shortening of the left ventricle are shown for the 2 groups.

greater extent than is baroreceptor control of sympathetic activity and systemic circulation.[9] However, in dogs with chronic heart failure induced by permanent stenosis of the pulmonary artery, occlusion of the common carotid arteries was accompanied not only by less tachycardia, but also by less pressor and vasoconstrictor responses than in control dogs.[10] Furthermore, we have recently observed (Grassi G, Seravalle G, and Mancia G, 1991) that in subjects with severe CHF (NYHA class III or IV), the increased and reduced mean arterial pressure obtained with intravenous infusions of phenylephrine and nitroprusside, respectively, is accompanied not only by no heart rate changes, but also by no changes in sympathetic nerve traffic, as assessed by microneurography in the peroneal nerve (Figure 3). Although caution should be exercised in extrapolating animal data to humans and sympathetic nerve traffic recorded in one district to another,[11] these observations suggest that the overall role of the baroreflex in cardiovascular homeostasis is compromised in CHF.

CARDIOPULMONARY REFLEX

The increased central blood volume and cardiac dilation characterizing CHF might benefit its neurohumoral pattern because volume-sensitive stretch receptors in the cardiopulmonary region inhibit sympathetic activity and secretion of renin and vasopressin.[4,12,13] Reflex influences from cardiopulmonary volume receptors, however, are abolished in severe,[14] and reduced in mild, CHF. This can be seen in Figure 4, which illustrates reflex increases in forearm vascular resistance in response to nonhypotensive reductions in central venous pressure induced by the application of mild negative pressures to the lower body in 6 patients with NYHA class II CHF. Compared with age-matched controls, the increases were less in heart failure patients and the differences were statistically signif-

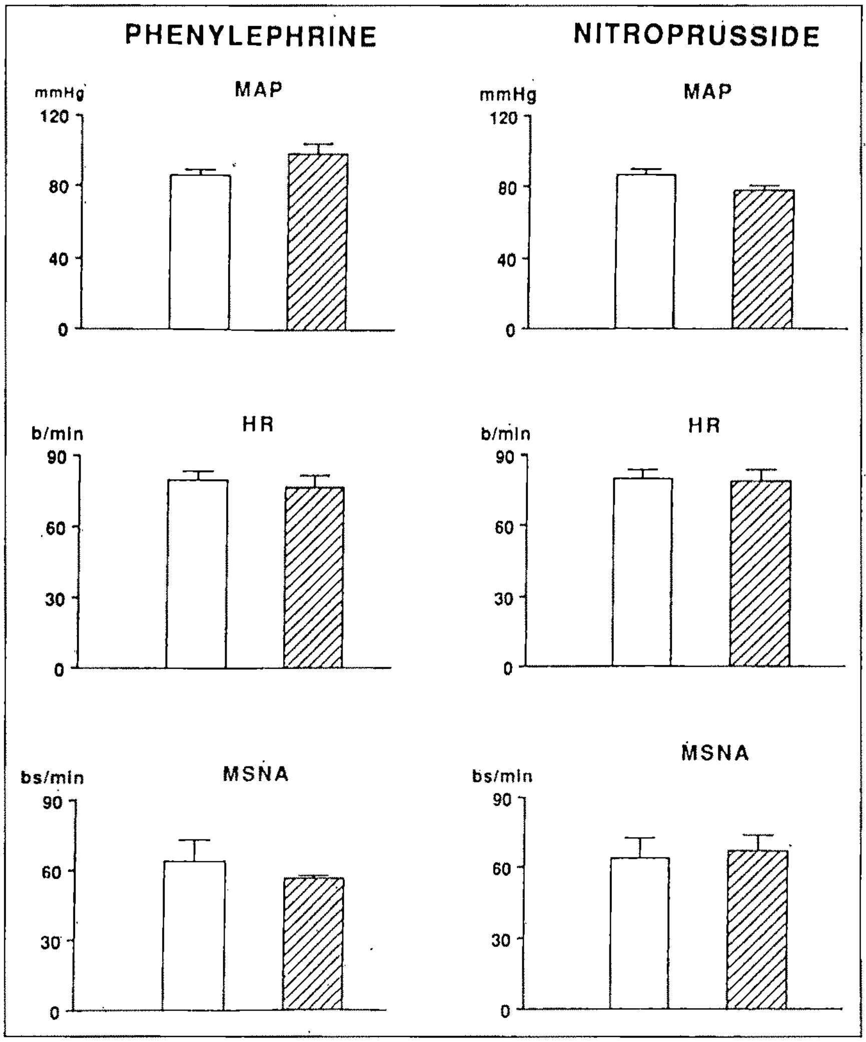


FIGURE 3. Effects of phenylephrine and nitroprusside intravenous infusions on mean arterial pressure (MAP), heart rate (HR), and muscle sympathetic nerve activity (MSNA) in 7 patients with congestive heart failure. Open histograms = control values; dashed histograms = values obtained during infusions. Data shown are mean ± standard error.

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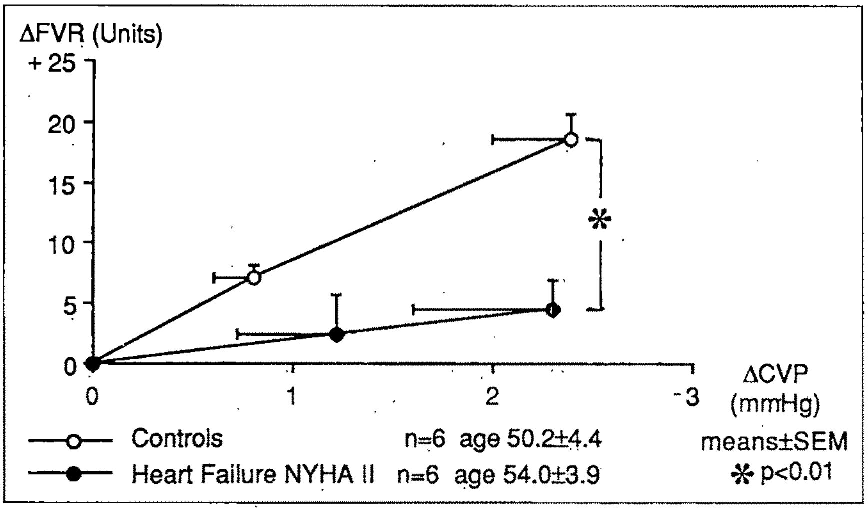

FIGURE 4. Reflex increases in forearm vascular resistance (FVR) induced by progressively reducing central venous pressure (CVP) via negative pressure to the lower body. Data are shown for control subjects and age-matched heart failure patients.

icant. Thus, in CHF the two major inhibitory influences exerted on the vasomotor center are impaired. This creates a state of "functional afferent denervation,"[15] which may well account for an increase in sympathetic drive.

MECHANISMS RESPONSIBLE FOR REFLEX IMPAIRMENT AND EFFECTS OF TREATMENT

Reduced baroreflex and cardiopulmonary sensitivity may be due to (1) a reduction in effector responsiveness to vagal and sympathetic stimuli, (2) a reduction in the receptor signal, and (3) an alteration of central reflex integration. All these abnormalities are likely to occur in CHF (Table I). Evidence from experimental models of CHF, however, indicates that a functional reduction in the receptor's ability to sense BP and blood volume plays an important role. This is emphasized in Figure 5, which shows that development in dogs of either high-output or low-output CHF is accompanied by a marked attenuation of the increase in atrial receptor activity.[16] Further disruption of the afferent receptor signal may occur as a result of the receptor destruction characteristic of heart failure.

Are the impaired baroreflex and cardiopulmonary reflex restored by treatment? This question has received a negative answer in reports of dogs with an arteriovenous fistula, in which impaired cardiac receptor activity was unaffected by reversal of CHF.[8] In other animal studies,[17] however, an improvement of the afferent signal has been reported. Further, shortly after heart transplantation, the baroreceptor–heart rate reflex has been shown to return to normal sensitivity.[18] Finally, an improvement of reflex cardiovascular control has been observed following administration of various drugs (Table II). The best results have been obtained with the digitalis glycosides, which mark-

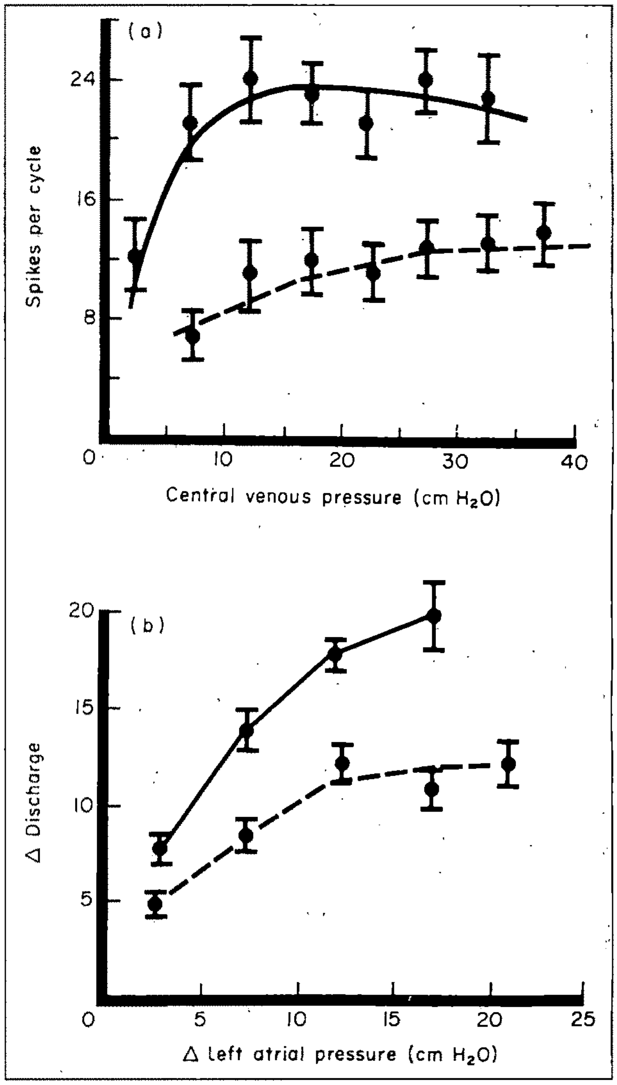

FIGURE 5. Firing rate of vagal fibers originating in the atria in response to increases in central venous pressure (*a*) or left atrial pressure (*b*) induced by volume expansion with dextran. Single fiber recordings from control dogs and dogs with low-output and high-output heart failure. Data shown are means ± standard error. (Reprinted with permission from *J Clin Invest*.[16])

TABLE I Reduced Baroreflex and Cardiopulmonary Reflex Sensitivity in Congestive Heart Failure

Reduced vagal/sympathetic effector responsiveness

Central factors (e.g., baroreflex impaired by increased angiotensin II levels)

Reduced receptor signal
  Receptor destruction
  Receptor desensitization
  Waterlogging
  Reduced vascular compliance

TABLE II Effects of Cardiovascular Drugs Used to Treat Congestive Heart Failure on Sympathetic Cardiovascular Control

Drug	Sympathetic Tone	Arterial Baroreflex	Cardiopulmonary Reflex
Hydralazine	↑	?	0
Dihydropyridines	↑ ?	→ ?	→ ?
ACE inhibitors	↓	↑ ?	?
Digitalis glycoside	↓	↑	↑

ACE = angiotensin-converting enzyme; ↓ = reduction, → = no change; ↑ = increase; ? = insufficient or conflicting information.

edly enhance the reflex responses obtained by manipulation of cardiopulmonary receptors,[19,20] as well as the vagal and sympathetic cardiac and vascular responses to baroreceptor manipulation.[21,22] Figure 6 shows the bradycardia and lengthening of atrioventricular conduction induced by increasing systolic BP with an intravenous bolus of phenylephrine, as well as the hypotensive response induced by stimulating carotid baroreceptors with a neck suction device.[21,22] Following an intravenous dose of acetyl-strophantidin, all responses were greater than before digitalis administration, and the differences were statistically significant. This may be due to a central action of digitalis glycosides, although a direct effect of the drug at the receptor site, e.g., an increased excitability due to activation of the ouabain sodium/potassium pump, is more likely to be involved.[23]

The fast and marked improvement of baroreflex and cardiopulmonary reflex sensitivity observed during surgical and pharmacologic treatment of CHF has pathophysiologic and clinical implications. Pathophysiologically, this improvement indicates that since reflex derangement is quickly reversible, its nature is functional rather than anatomic. The clinical implication is that this increased reflex sensitivity favors attenuation of the sympathetic and renin-angiotensin hyperactivity of CHF.[2,24,25] Because this hyperactivity is related to survival,[2,24,25] this may have an impact on improving the prognosis for patients with CHF.

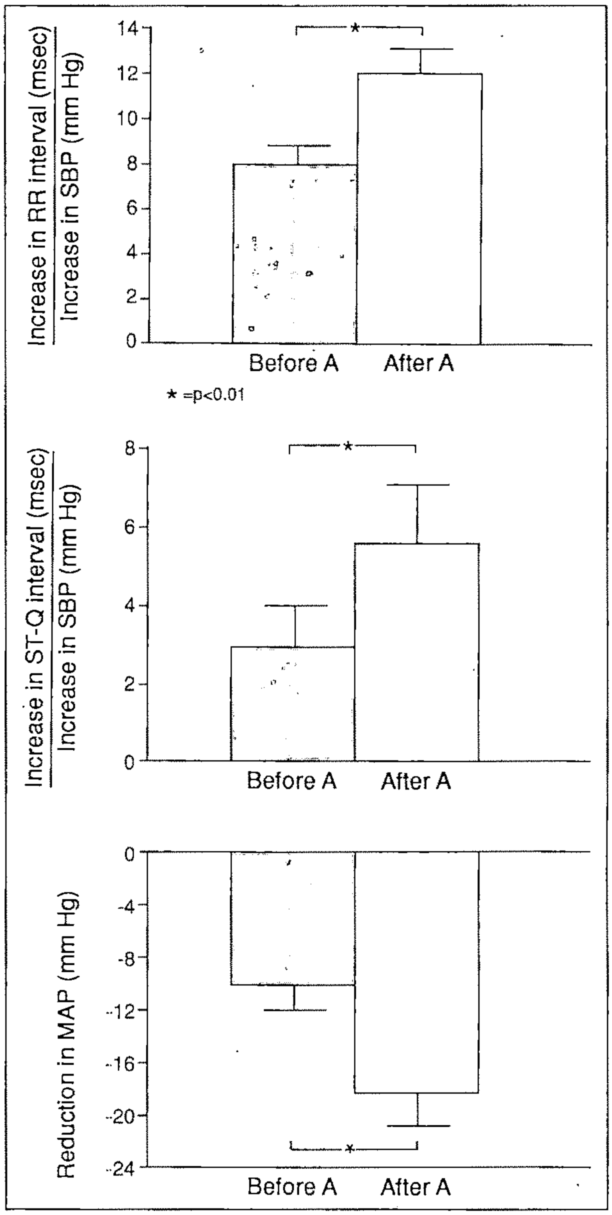

FIGURE 6. Changes in R-R interval, atrioventricular conduction time and mean arterial pressure (MAP) obtained by increasing systolic blood pressure (SBP) with an intravenous bolus of phenylephrine (*top* and *center* panels) or by increasing carotid transmural pressure with a neck chamber device (*bottom* panel). Bars represent findings in normal subjects before (Before A) and after (After A) an intravenous injection of acetyl-strophanthidin. Data shown are mean ± standard error. A = acetyl-strophanthidin (digitalis glycoside). (Modified from *Cardiovasc Res.*[22])

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DISCUSSION

Dr. Gheorghiade: It appears that currently, digitalis glycosides are being challenged as the drug of choice in controlling ventricular rate in patients with atrial fibrillation, since it is believed that the only effect of the drug on the atrioventricular (AV) node is vagally mediated and thus the effect is lost during exercise. Based on what you said, is there more than just a vagal effect (i.e., concealed conduction)?[1]

Dr. Mancia: Baroreflex enhancement by digitalis glycosides involves not only vagally mediated but also sympathetically mediated responses. However, baroreceptor modulation of AV conduction is entirely mediated via the vagus, since reflex changes are abolished by atropine. So the fact seems to be that digitalis glycosides markedly improve vagal tone through an increase in baroreflex sensitivity.

Dr. Gheorghiade: What are the effects of exercise on heart rate in patients with atrial fibrillation who are fully digitalized?

Dr. Mancia: We studied baroreceptor control of heart rate at rest and during exercise. During exercise, a large fraction of this control was lost (probably because the central command interfered with central baroreflex integration) so that it may be true that in physically active patients some of the benefits due to enhancement of the baroreflex by digitalis glycosides are less evident.

Dr. Creager: I wanted to explore with you the mechanisms for arterial baroreceptor dysfunction. We looked at carotid artery compliance directly, using ultrasound, and found that such compliance is, without question, diminished in patients with heart failure. Wang et al [2] have just published an article in which carotid artery compliance was studied in ventricular-paced dogs with carotid baroreceptor dysfunction. They make a case, at least in ventricular-paced dogs in heart failure, that there are abnormalities of sodium–potassium adenosine triphosphatase (Na^+,K^+-ATPase) and noncompliance. I would like to review in a bit more detail whether you think any of these mechanisms are pertinent and, if not, what might apply?

Dr. Mancia: There is no question that changes in cardiac and vascular structure may be involved. We know, for example, that cardiac hypertrophy, i.e., a common condition in congestive heart failure (CHF), impairs the cardiogenic reflex.[3] In addition, as you mention, arterial compliance seems to be reduced in CHF and we have seen that this can indeed be a striking change. Functional mechanisms may also play a role, however, and one mechanism may be high levels of angiotensin II, because angiotensin II adversely affects baroreflex sensitivity.[4] I do not know why digitalis glycosides enhance baroreflex and cardiopulmonary reflex sensitivity, but it is clear that we have to take into account that reflex modulation of both vagus and sympathetic activity is involved.[4] I am inclined to think that an important factor is sensitization of receptors themselves and indeed Gillis and Quest[5] have shown this to occur in cats with isolated carotid sinuses exposed to digitalis glycosides.

Dr. Gheorghiade: Trimarco et al [6] have shown that some patients with coronary artery disease and preserved left ventricular (LV) function may have an abnormality in their baroreceptor sensitivity. In these patients, impaired low-pressure-receptor responsiveness was associated with prolonged duration of myocardial ischemia in Holter monitoring. When the cardiopulmonary reflexes were restored by digitalis glycoside preparations, the duration of myocardial ischemia was reduced.

Dr. Mancia, do you have any evidence to indicate that baroreceptor function may be abnormal in patients very early in the course of LV dysfunction? If so, would it be wise to treat these patients with agents that will improve cardiopulmonary reflex sensitivity?

Dr. Mancia: Your question would be answered by studying the baroreflex and the cardiopulmonary reflex in subjects ranging from mild to severe CHF, possibly looking at asymptomatic heart failure as well. We are doing this, but the number so far collected is not enough to reach a conclusion.

Concerning the effect of myocardial infarction, we have seen that 2 days after admission to the coronary care unit, the baroreflex is impaired.[7] The cardiopulmonary reflex is also impaired after the acute coronary episode[8] but both reflex functions eventually recover and thus we do not have evidence of a permanent reflex alteration. I should emphasize, however, that we studied patients with no obvious hemodynamic derangement and thus cannot exclude the possibility that whenever the myocardial infarction causes a myocardial dysfunction, a sustained reflex impairment takes place. This may be the explanation of the sustained baroreflex impairment reported by Schwartz et al[9] in a few subjects with myocardial infarction.

Dr. Gheorghiade: Was this reduction related to changes in LV function?

Dr. Mancia: Acutely, it was not. Chronically, we do not know.

Dr. Gheorghiade: In patients with asymptomatic LV dysfunction, is there a correlation between plasma norepinephrine concentrations, plasma renin activity, and baroreceptor function?

Dr. Ferguson: In most of the clinical studies in patients who have established heart failure, the only evidence we have is that the degree of impairment of baroreflex-mediated vasoconstrictor responses between moderate and severe heart failure appears to be similar.

Dr. Mancia: I think this is a difficult question to answer also because it is not easy to classify mild CHF. In the study I showed, for example, patients were in NYHA class II, but echocardiographic data were such as to doubt that they indeed had a mild heart failure condition. It would obviously be important to see whether there is a correlation between the increase in plasma norepinephrine and renin levels and the impairment of the baroreflex. Probably, however, more data are needed to make it meaningful.

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Digitalis and Neurohormonal Abnormalities in Heart Failure and Implications for Therapy

David W. Ferguson, MD

A pathophysiologic hallmark of heart failure is neurohormonal excitation, a prominent feature of which is activation of the sympathetic nervous system. Studies from our laboratories demonstrate that clinical heart failure is characterized by marked increases in efferent sympathetic neural outflow to muscle; the magnitude of this sympatho-excitation parallels the degree of cardiac dysfunction. Impairments of cardiopulmonary and arterial baroreflex sensory mechanisms appear to be responsible to a significant degree for this sympatho-excitation, consistent with findings in animal models of heart failure. Digitalis glycosides exert modest inotropic actions when administered to patients with heart failure. Digitalis also has potent autonomic effects that can potentiate impaired arterial and cardiopulmonary baroreflex mechanisms in experimental models of cardiac dysfunction. Acute digitalis administration to patients with moderate-to-severe heart failure produces profound and sustained sympatho-inhibition, which precedes any observed hemodynamic action of the agent. Further, acute digitalization of such patients rapidly normalizes impaired baroreflex-mediated mechanisms. Data now suggest that the mechanism of action of digitalis in humans is an acute potentiation of baroreceptor-mediated afferent regulation of sympathetic neural mechanisms. Prospective, randomized and controlled studies now are required to test the hypothesis that the acute effects of digitalis on autonomic mechanisms also are observed during chronic administration. In theory, the chronic sympatho-inhibitory action of digitalis, combined with its chronic potentiation of impaired baroreflex mechanisms, may offer beneficial effects independent of its inotropic actions in patients with heart failure.

(Am J Cardiol 1992;69:24G–33G)

Heart failure is a clinical problem of increasing magnitude. More than 2.5 million U.S. citizens currently have this disorder, and 400,000 new cases are diagnosed yearly. The mean life expectancy of these patients is 5 years, although those having the most severe heart failure survive less than 1 year on average. A pathophysiologic characteristic of heart failure is neurohormonal activation, demonstrated by markedly elevated circulating levels of norepinephrine, aldosterone, arginine vasopressin, and atrial natriuretic factor, as well as increased activity of the renin–angiotensin–aldosterone system.[1–3] Although initially considered an adaptive response to impaired cardiac output and/or vascular congestion, contemporary thought suggests that activation of these neuroendocrine responses is often maladaptive (resulting from mechanisms intended to protect the organism from hypovolemic hypotension, but potentially inappropriate in the setting of heart failure). Recent data from the Studies of Left Ventricular Dysfunction (SOLVD) indicate that such neurohumoral excitation actually precedes the clinical onset of heart failure.[4] The magnitude of neuroendocrine activation appears to reflect (and possibly affect) inversely the prognosis of these patients.[5,6]

Numerous experimental and clinical studies have examined the potential mechanisms responsible for these abnormalities and are summarized in a prior review.[7] This article summarizes studies from our laboratories at the University of Iowa that have attempted to examine the mechanisms underlying neurohormonal activation in patients with heart failure and the potential for digitalis glycosides to influence these mechanisms.

SYMPATHO-EXCITATION IN HUMAN HEART FAILURE

A prominent component of neurohormonal activation in heart failure is marked excitation of the sympathetic nervous system, traditionally indicated by increased levels of circulating norepinephrine. Potential mechanisms for the increased norepinephrine include augmented adrenomedullary release of catecholamine, increased efferent sympa-

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thetic outflow from the central nervous system, facilitated release of norepinephrine from peripheral sympathetic nerve terminals, and/or alterations of peripheral reuptake and metabolism of the neurotransmitter.

Using percutaneous microneurography for direct assessment of efferent muscle sympathetic nerve activity, recent studies from our laboratories have shown that increased central sympathetic neural outflow characterizes clinical heart failure and is a major component of sympatho-excitation in this disorder. Percutaneous microneurography allows direct, quantitative, sensitive, and reproducible recordings of multifiber, postganglionic, efferent sympathetic nerve activity from peripheral nerves in intact humans at rest, during cardiovascular perturbations such as exercise and simulated orthostasis and in response to acute pharmacologic interventions.[8] Muscle sympathetic nerve activity is regulated primarily by baroreflex, chemoreflex, and somatic reflex mechanisms. Therefore, the microneurographic technique provides a unique assessment of one of the neuroeffector limbs involved in these reflex mechanisms.

Leimbach and colleagues[9] were the first to demonstrate, in a small number of patients, that heart failure is accompanied by significant increases in resting sympathetic nerve activity to skeletal muscle. More recent studies by Ferguson et al,[10] in a larger group of patients with moderate-to-severe heart failure, have confirmed and extended these initial observations. Compared with normal subjects, patients with heart failure have markedly increased levels of sympathetic nerve activity (Figure 1).[10] This increase in pulse-synchronous neural activity is not simply a reflection of the increased heart rate observed in these patients (Figure 2).[10] Multiple linear regression analyses indicate that the magnitude of increase in efferent sympathetic neural outflow to muscle parallels the impairment of cardiac performance. Muscle sympathetic nerve activity is most strongly and inversely correlated with left ventricular stroke work index and stroke volume index, and positively correlated with pulmonary artery diastolic and mean pressures (Figure 3).[10] No correlation has been observed between resting sympathetic nerve activity and mean arterial pressure, left ventricular ejection fraction, cardiac chamber size, or arterial oxygen tension. These studies also demonstrate a close correlation between muscle sympathetic nerve

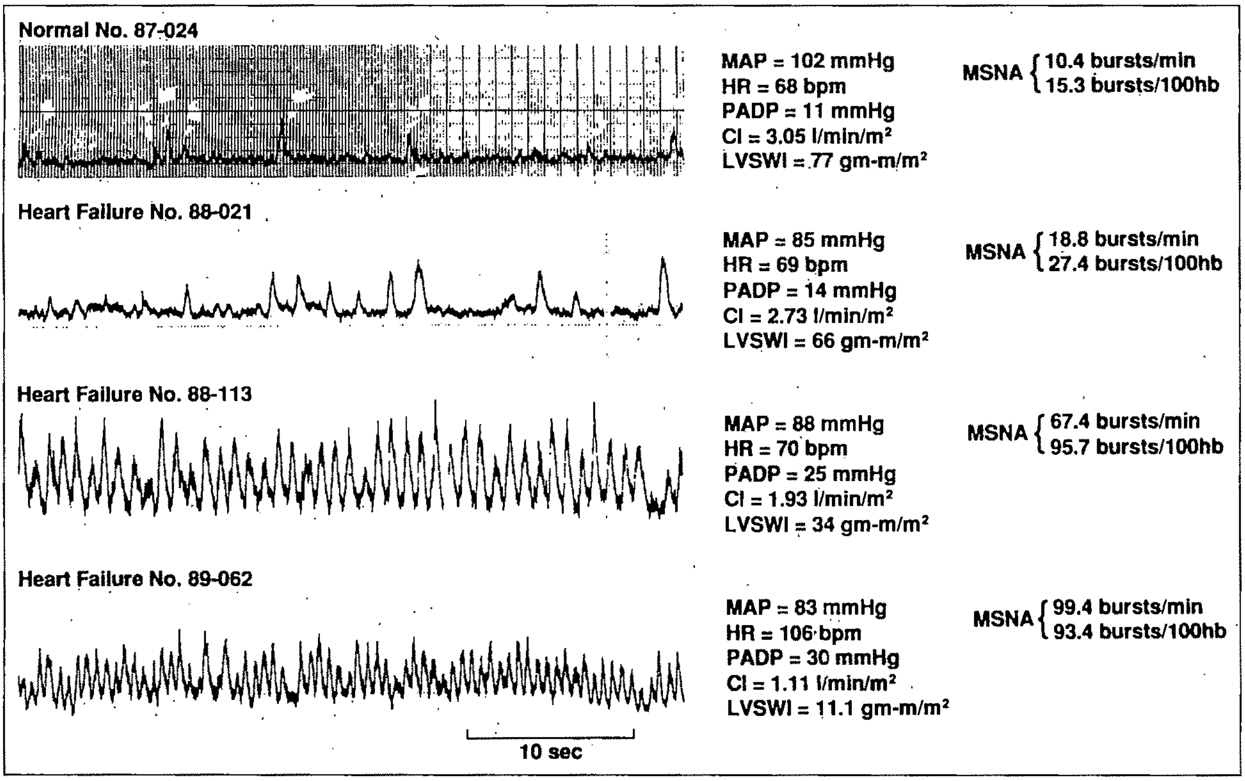

FIGURE 1. Experimental recordings of muscle sympathetic nerve activity (MSNA) in a normal subject (*upper panel*), a patient with mild heart failure (*second panel* from top) and 2 patients with severe heart failure (*lower panels*). Increased MSNA at rest is seen in patients with more severe cardiac impairment. bpm = beats per minute; CI = cardiac index; hb = heart beats; HR = heart rate; LVSWI = left ventricular stroke work index; MAP = mean arterial pressure; PADP = pulmonary artery diastolic pressure. (Reproduced with permission from *J Am Coll Cardiol*.[10])

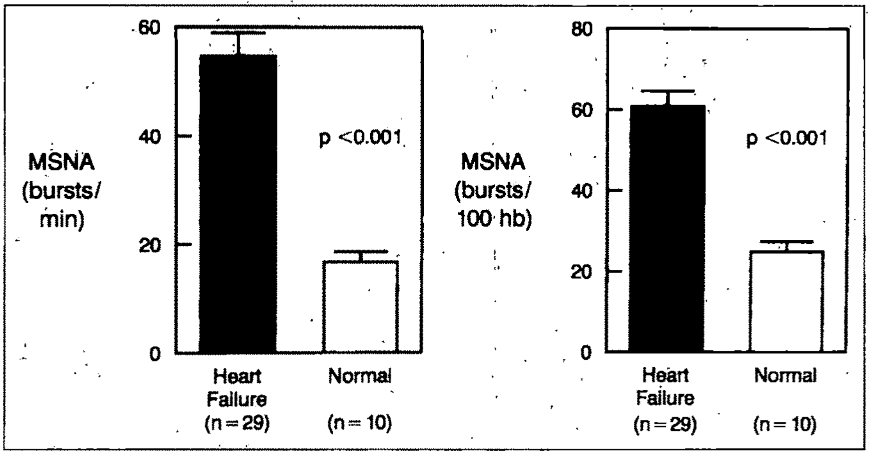

FIGURE 2. Bar graphs comparing muscle sympathetic nerve activity (MSNA) at rest in 29 patients with heart failure and 10 normal subjects. Patients with heart failure have significantly higher levels of MSNA expressed as bursts per minute (*left panel*). This increase is not related to variation in heart rate, since the difference persists when sympathetic activity is corrected for heart rate (*right panel*). Data are mean ± standard error of the mean. hb = heart beats. (Reproduced with permission from *J Am Coll Cardiol.*[10])

activity and plasma norepinephrine levels in resting patients with heart failure (Figure 4).[10]

Mechanisms underlying sympathetic excitation in heart failure Regulation of efferent sympathetic and parasympathetic outflow from the brainstem's vasomotor centers depends on afferent input from a number of peripheral sensory influences. These can be broadly classified as *inhibitory* and *excitatory* afferent mechanisms. A tonic inhibitory afferent modulation is exerted by mechanosensitive receptors located predominantly in the left ventricle, left atrium, and venoatrial regions (cardiopulmonary baroreceptors), as well as in the aortic arch and carotid sinus regions (arterial baroreceptors). Excitatory afferent modulation is exerted by chemosensitive receptors in the carotid sinus region (arterial chemoreceptors) and metaboreceptors in muscle beds that are activated by ischemic metabolites during exercise. Detailed animal studies have demonstrated impairment of the afferent inhibitory influence of cardiopulmonary and arterial baroreceptors in experimental heart

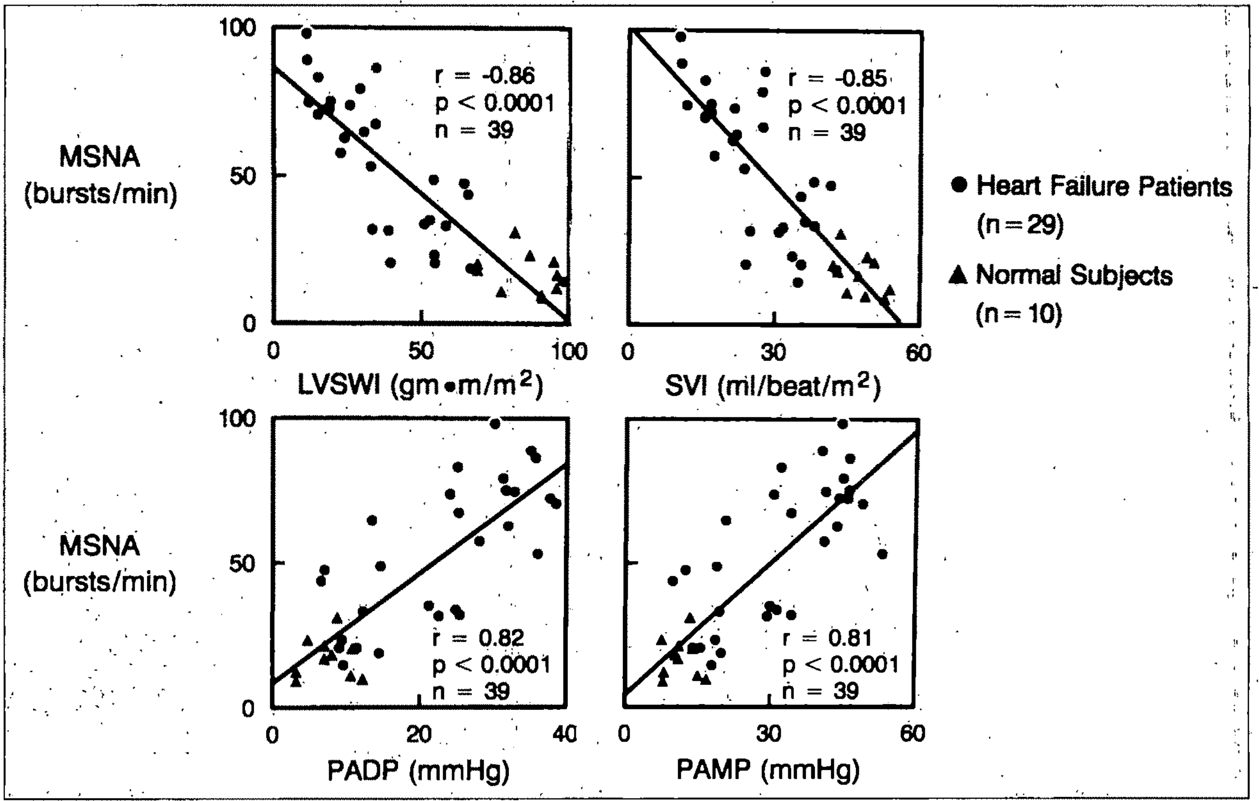

FIGURE 3. Correlations between resting muscle sympathetic nerve activity (MSNA) and hemodynamic variables in 10 normal subjects (▲) and 29 patients with heart failure (●). There were strong inverse correlations between MSNA and left ventricular stroke work index (LVSWI) and stroke volume index (SVI). Strong positive correlations were determined between MSNA and pulmonary artery diastolic (PADP) and mean (PAMP) pressures. (Reproduced with permission from *J Am Coll Cardiol.*[10])

failure.[7] Clinical studies[7] in our laboratories are consistent with the concept of attenuated afferent inhibitory-baroreflex impairment in patients with heart failure.

Results of the previously cited studies, which showed markedly increased efferent sympathetic nerve activity in heart failure patients during rest and in the absence of hypoxemia, acidemia, or hypercapnia, suggest that the augmented influence of excitatory (e.g., chemoreceptor or muscle metaboreceptor) afferents alone likely does not explain the sympatho-excitation characteristic of heart failure.[10] Comparison of forearm vasoconstrictor responses to orthostatic stress in normal humans and patients with heart failure provide supportive evidence implicating impairment of cardiopulmonary baroreceptor function in clinical heart failure.[11] When exposed to stimulated orthostatic stress produced by lower-body negative pressure (which reduces cardiac preload and therefore primarily "unloads" cardiopulmonary baroreceptors), normal humans demonstrate sympathetically mediated forearm vasoconstriction (Figure 5).[11] In contrast, patients with heart failure have significantly elevated forearm vascular resistance at rest, consistent with neurohormonal excitation in this disorder. Under similar amounts of lower-body negative pressure, these patients fail to exhibit vasoconstrictor responses and tend to develop paradoxic vasodilation (Figure 5). Such impairment appears selective for baroreflex-mediated responses, since the same patients have intact vasoconstrictor responses to nonbaroreflex-mediated stimuli such as the cold pressor test and to intra-arterial infusion of norepinephrine (Figure 6).[11]

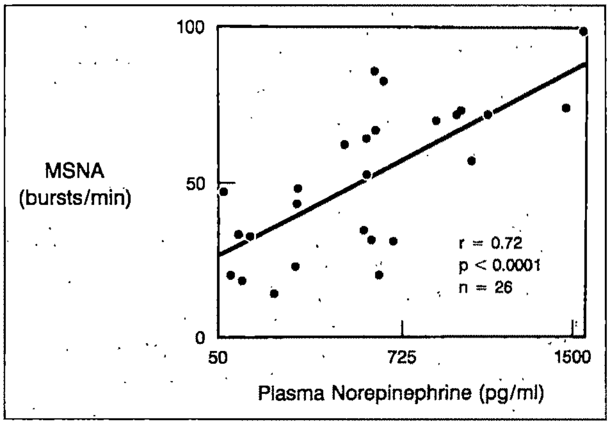

FIGURE 4. Correlations between resting muscle sympathetic nerve activity (MSNA) and plasma norepinephrine levels in 26 patients with heart failure. There is a strong positive correlation between direct measurements of these 2 parameters of the efferent sympathetic nervous system. (Reproduced with permission from *J Am Coll Cardiol*.[10])

Studies using microneurography have provided additional support for the concept of impaired baroreflex-mediated responses in patients with heart failure.[12] Compared with normal subjects, patients with heart failure demonstrate impaired sympatho-inhibitory responses to baroreceptor activation produced by phenylephrine infusion and significant impairment of sympatho-excitatory responses to infusion of the vasodilating agent sodium nitroprusside (Figures 7 and 8).[12] The high baseline sympathetic nerve activity in heart failure patients does not appear to explain the attenuated sympatho-excitatory response to nitroprusside, because similarly affected patients have shown intact sympatho-excitatory responses to nonbaroreflex-mediated stimuli such as the cold pressor test (Figure 9).[13]

Thus, experimental observations in patients with heart failure are consistent with those in animal models and support the concept that abnormal baroreflex mechanisms are likely responsible to a significant degree for the activation of the sympathetic nervous system in this disorder. An attenuation of such baroreflex mechanisms, with loss of the normal, tonically active, afferent inhibitory influence of cardiopulmonary and/or arterial baroreflexes on the brainstem cardiovascular centers, would be expected to result in an increase in efferent sympathetic neural outflow.

Recently, new insight has been gained regarding the effect of digitalis glycosides on these afferent mechanisms. The theory is now emerging that

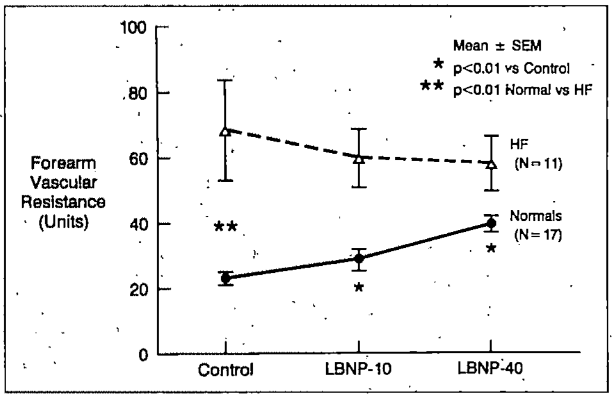

FIGURE 5. Responses of normal subjects and patients with heart failure (HF) to unloading (deactivation) of baroreceptors with orthostatic stress produced by lower-body negative pressure (LBNP) at −10 mm Hg (LBNP-10) and at −40 mm Hg (LBNP-40). Control forearm vascular resistance (venous occlusion plethysmography) was significantly higher in the heart failure patients than in the normal subjects. Normal subjects developed significant forearm vasoconstriction during LBNP (manifested by an increase in forearm vascular resistance). In contrast, patients with heart failure failed to vasoconstrict and tended to experience paradoxic vasodilation. (Reproduced with permission from *Circulation*.[11])

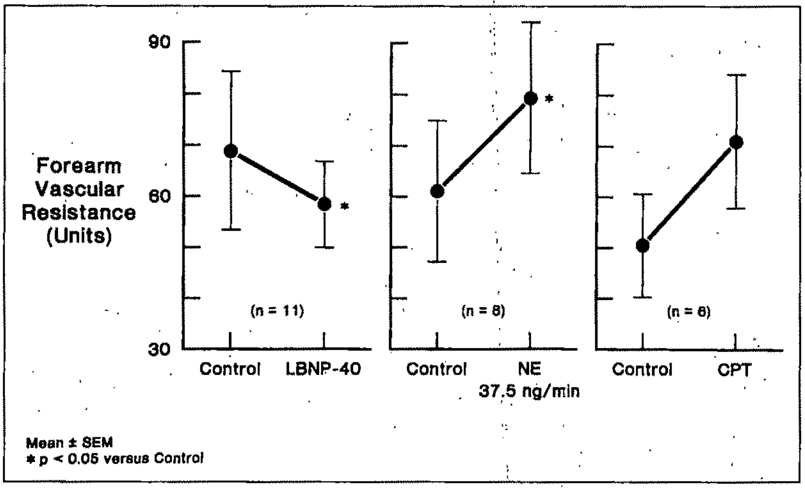

FIGURE 6. Comparison of forearm vascular responses of patients with heart failure to orthostatic stress produced by lower-body negative pressure (LBNP) at − 40 mm Hg (LBNP-40), intra-arterial infusion of norepinephrine (NE) into the forearm at 37.5 ng/min and to the cold pressor test (CPT) performed with immersion of the contralateral hand in ice water. Patients developed normal vasoconstrictor responses to infusion of the neurotransmitter norepinephrine and tended to have vasoconstriction during the CPT. In contrast, the same patients failed to vasoconstrict and actually tended to vasodilate during baroreceptor unloading with LBNP. These results are consistent with a selective impairment of baroreflex-mediated vasoconstrictor responses in patients with heart failure. (Reproduced with permission from *Circulation*.[11])

digitalis, in addition to its established role as a modest inotropic drug, may have beneficial effects in patients with heart failure via its autonomic modulating actions.

AUTONOMIC ACTIONS OF DIGITALIS GLYCOSIDES IN HEART FAILURE

Digitalis glycosides have played an important, although controversial, role in the management of patients with heart failure for more than 2 centuries. Despite alternating periods of enthusiasm and hesitancy regarding the efficacy of these agents, recent prospective, randomized, controlled trials[14] have demonstrated therapeutic advantages in most patients with moderate-to-severe heart failure who are in sinus rhythm. In general, efficacy has been attributed to the inotropic properties of digitalis. Extensive studies in animals, however, indicate that digitalis glycosides also have significant and potentially clinically relevant autonomic and central nervous system actions, exerting their effects at numerous sites in the neurocardiovascular axis. Although an elaboration is beyond the scope of this article, data reveal that digitalis exerts sympatho-inhibitory actions via potentiation of afferent baroreflex mechanisms, sympatho-excitatory ac-

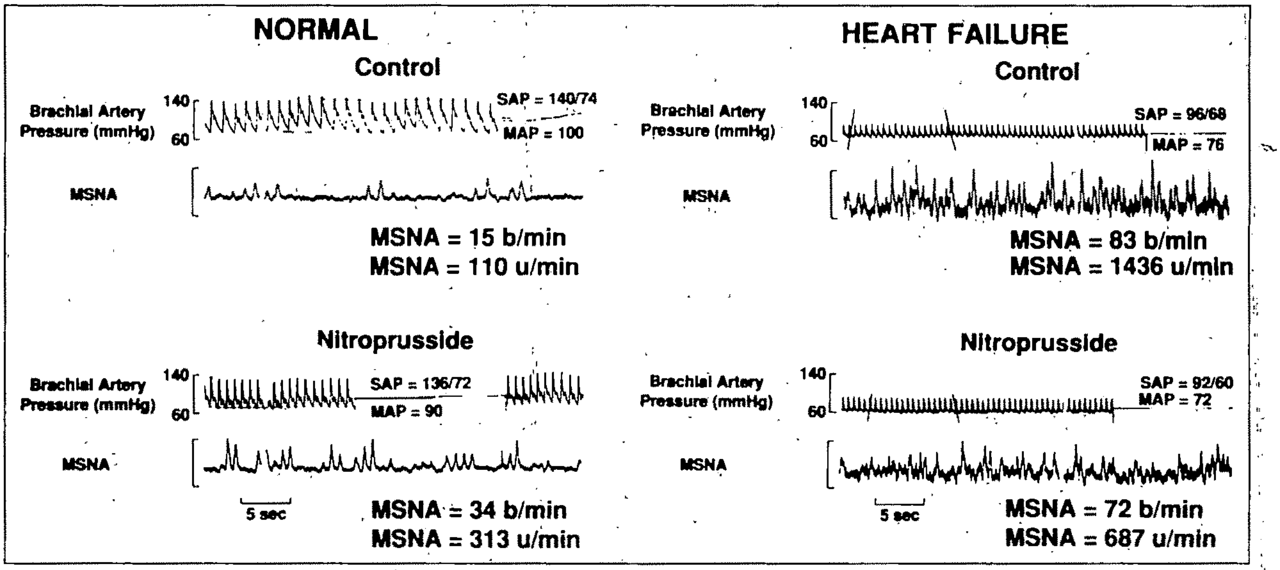

FIGURE 7. Comparative experimental recordings from a normal subject (*left panels*) and heart failure patient (*right panels*) during control conditions (*upper panels*) and baroreceptor unloading with intravenous nitroprusside (*lower panels*). Despite similar nitroprusside-induced decreases in arterial pressure and cardiac filling pressure, the normal subject demonstrated significant increases in muscle sympathetic nerve activity (MSNA), whereas the heart failure patient did not exhibit sympatho-excitation. In the heart failure patient, nitroprusside actually produced a decrease in sympathetic burst frequency and total integrated sympathetic activity. SAP = systemic arterial pressure; MAP = mean arterial pressure; b/min = bursts per minute; u/min = units per minute. (From *Am J Cardiol*.[12])

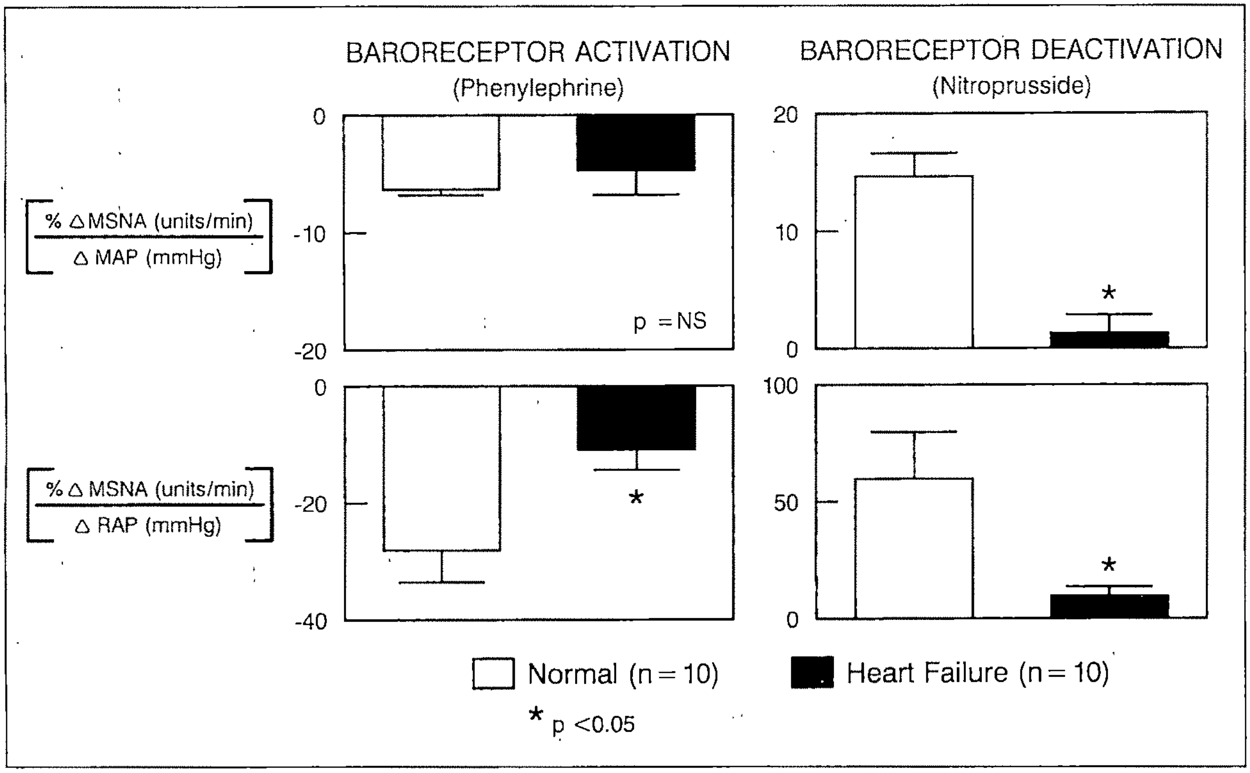

FIGURE 8. Comparison of baroreflex sympathetic sensitivity of normal subjects and heart failure patients in response to baroreceptor activation (intravenous phenylephrine, *left panels*) and deactivation (intravenous nitroprusside, *right panels*). Heart failure patients appeared to have an attenuation of sympatho-inhibitory responses to baroreceptor activation when expressed as percent decrease in total integrated muscle sympathetic nerve activity (MSNA) per absolute increase in right atrial pressure (RAP). More strikingly, heart failure patients demonstrated marked attenuation of sympatho-excitatory responses to baroreceptor deactivation when expressed as percent increase in total integrated MSNA per absolute decrease in mean arterial pressure (MAP) or RAP. Values are mean ± standard error of the mean. (From *Am J Cardiol.*[12])

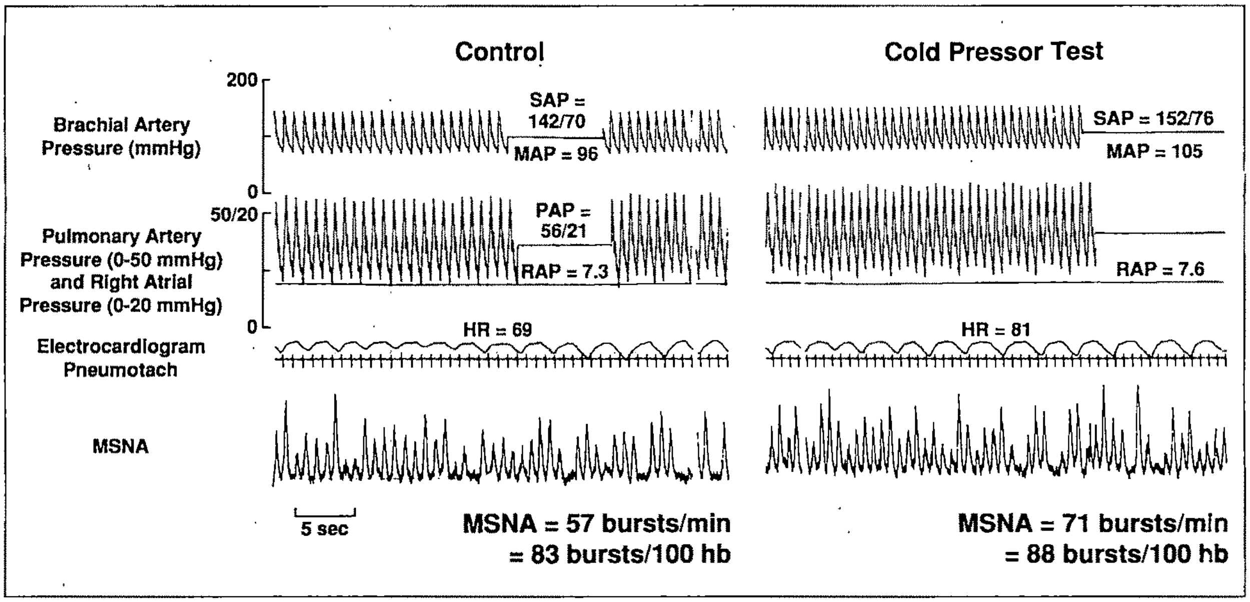

FIGURE 9. Experimental recordings from a patient with heart failure before (control) and during the cold pressor test. In this patient, hand immersion in ice water produced increases in systolic (SAP) and mean (MAP) arterial pressures, heart rate (HR) and pulmonary artery pressure (PAP), with minimal change in right atrial pressure (RAP). Hand immersion in ice water produced increases in muscle sympathetic nerve activity (MSNA) that were not related to the increase in heart rate, as demonstrated by the increase in MSNA when corrected for corresponding increase in heart beats (hb). (From *Am J Cardiol.*[13])

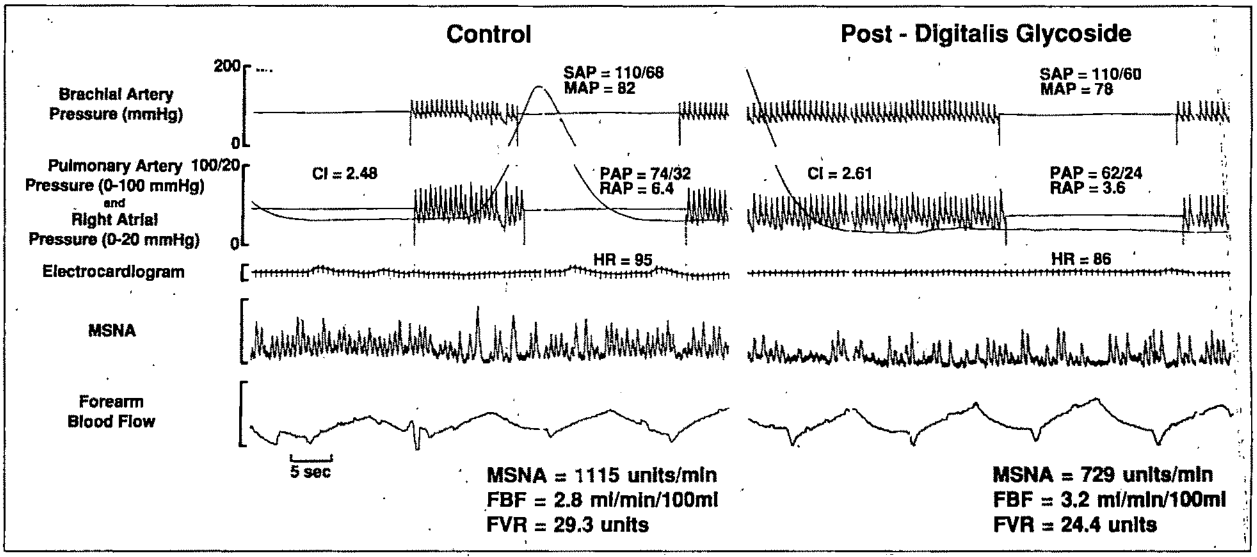

FIGURE 10. Experimental recordings from a heart failure patient obtained before (control) and following intravenous administration of deslanoside 0.02 mg/kg. Given intravenously, this digitalis preparation produced a significant increase in cardiac index (CI) and decrease in both right atrial (RAP) and pulmonary artery (PAP) pressures, as well as a slowing of heart rate (HR). A forearm vasodilatory response, indicated by an increase in forearm blood flow (FBF) and decrease in forearm vascular resistance (FVR), and a marked inhibition of efferent muscle sympathetic nerve activity (MSNA) were also observed. SAP = systemic arterial pressure; MAP = mean arterial pressure. (Reproduced with permission from *Circulation*.[15])

tion via central mechanisms and both adrenergically mediated and direct vasoconstrictor effects on vascular smooth muscle.

Studies from our laboratories of patients with heart failure support these findings. Using direct microneurographic recordings of efferent sympathetic nerve activity in muscle, the effects of short-term digitalis administration were examined in patients with moderate-to-severe heart failure.[15] Intravenous administration of a rapidly acting digitalis preparation (deslanoside [Cedilanid-D]) produced profound sympatho-inhibition and peripheral vasodilation in these patients (Figure 10 and 11). The early and sustained reduction in sympathetic nerve activity following intravenous digitalization preceded any observed hemodynamic effects of the agent. Importantly, these sympatho-inhibitory effects did not appear to be due simply to the drug's inotropic actions, since administration of dobutamine in other heart failure patients did not alter sympathetic nerve activity despite producing similar inotropic actions (Figure 12).

Further insight has recently been derived by examining the effects of digitalis on responses to unloading (deactivation) of cardiopulmonary

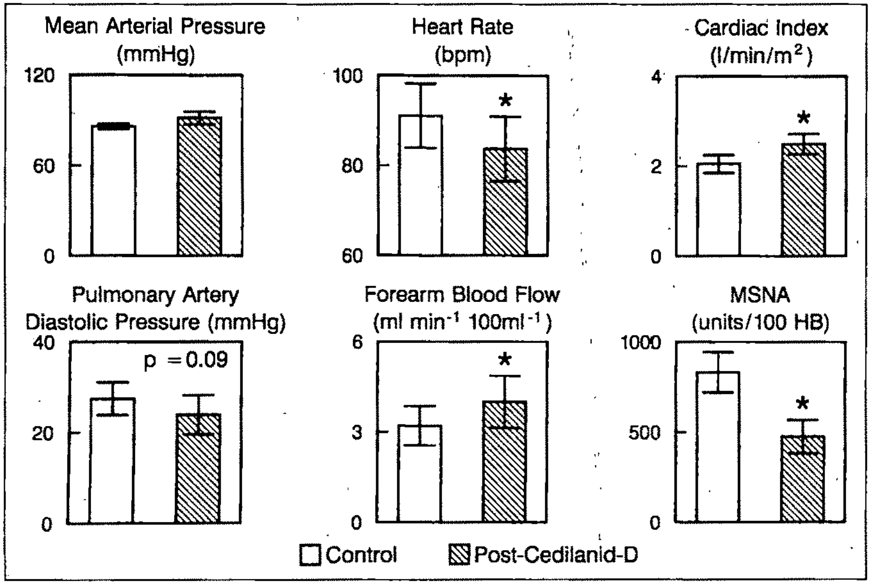

FIGURE 11. Bar graphs of hemodynamic and muscle sympathetic nerve activity (MSNA) following acute administration of a digitalis glycoside (deslanoside [Cedilanid-D]) in 8 heart failure patients. Results showed significant increases in cardiac index and forearm blood flow, decrease in heart rate and tendency for decrease in pulmonary artery diastolic pressure. There was also a profound attenuation of efferent muscle sympathetic nerve activity (MSNA). Data are mean ± standard error of the mean. HB = heart beats; bpm = beats per minute. (Reproduced with permission from *Circulation*.[15])

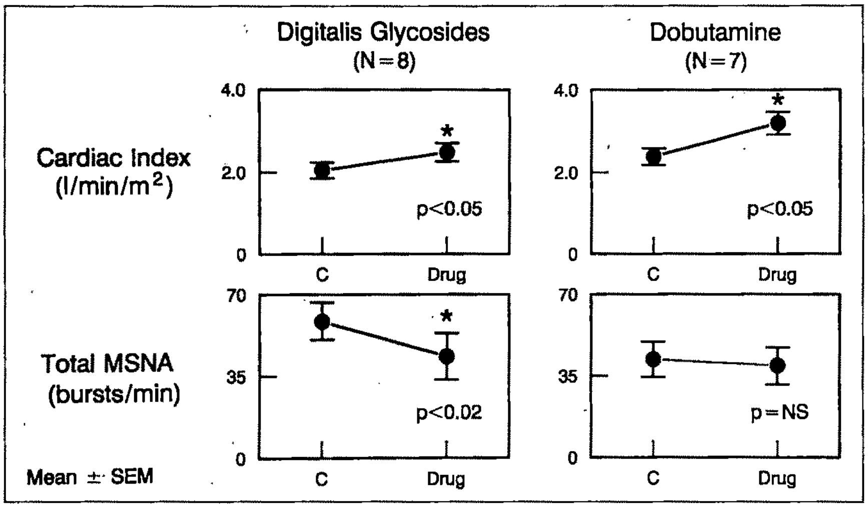

FIGURE 12. Comparative inotropic and sympathetic neural responses of heart failure patients to intravenous administration of digitalis glycosides vs administration of dobutamine. Although both treatment groups had similar increases in cardiac index, heart failure patients receiving digitalis developed profound decreases in efferent sympathetic nerve activity (sympatho-inhibition) whereas no such effect was observed in those given dobutamine. These data suggest that the sympatho-inhibitory response following acute digitalization in heart failure patients cannot be ascribed solely to the drug's inotropic action. MSNA = muscle sympathetic nerve activity. (Reproduced with permission from *Heart Failure*.[7])

baroreceptors with simulated orthostatic stress produced by lower-body negative pressure. Microneurographic recordings showed that digitalis (but not dobutamine or placebo) selectively potentiated sympathetic neural responses to this baroreflex perturbation in normal humans (Figure 13).[16] In contrast, digitalis did not alter sympathetic nerve responses to the cold pressor test, suggesting a selective potentiation of cardiopulmonary baroreflex regulation of sympathetic neural responses in normal humans. Similarly, using forearm vasoconstrictor responses as an index of efferent sympa-

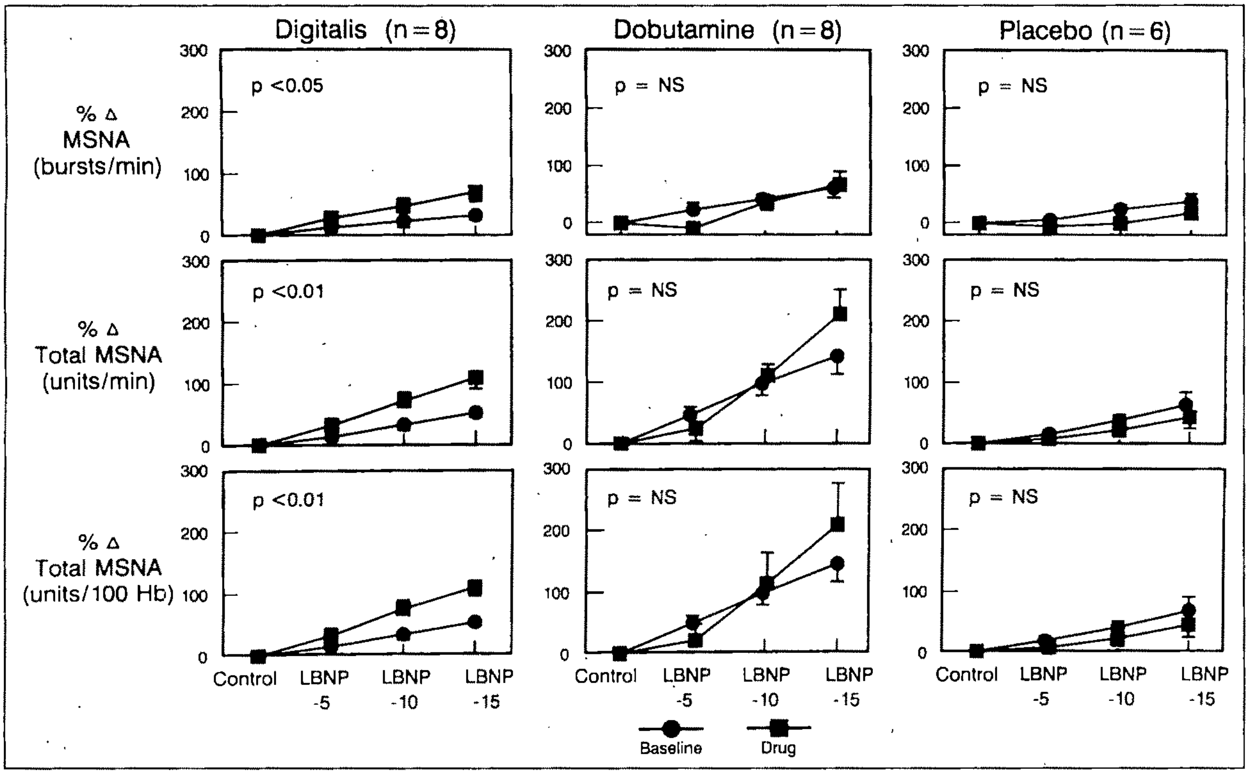

FIGURE 13. Graphs show comparison of effects of digitalis (*left panels*), dobutamine (*middle vertical panels*) and placebo (*right panels*) on muscle sympathetic nerve activity (MSNA) responses to cardiopulmonary baroreceptor unloading with lower-body negative pressure (LBNP). The sympatho-excitatory responses to cardiopulmonary baroreceptor deactivation, expressed as MSNA burst frequency (*upper panels*), percent change in total integrated MSNA (*middle horizontal panels*) and percent change in total MSNA corrected for heart rate (*lower panels*), were potentiated by digitalis but not altered by dobutamine or placebo (repeated measured by analysis of variance). Values are mean ± standard error of the mean. LBNP-5 = LBNP at − 5 mm Hg; Hb = heart beats; NS = not significant. (Reproduced with permission from *Circulation*.[15])

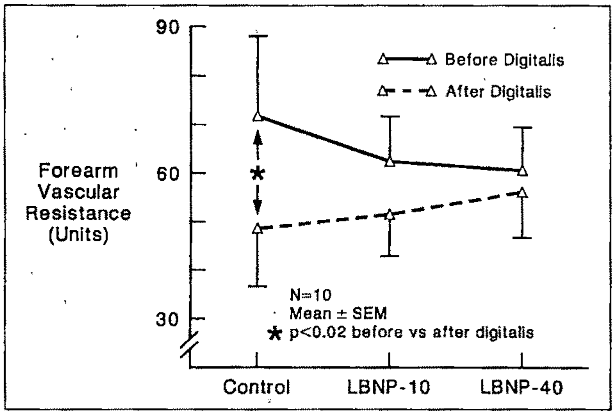

FIGURE 14. Forearm vasoconstrictor responses of heart failure patients during orthostatic stress produced by lower-body negative pressure at − 10 mm Hg (LBNP-10) and − 40 mm Hg (LBNP-40) performed before and following intravenous administration of cardiac glycoside. In the predrug state, heart failure patients developed paradoxic vasodilation during unloading of baroreceptors with LBNP. Following digitalis administration, control (pre-LBNP) forearm vascular resistance was lower, and vasoconstrictor response to orthostatic stress was normal. (Reproduced with permission from *Heart Failure*.[7])

thetic responses to simulated orthostatic stress, studies in heart failure patients demonstrated that acute digitalis administration reduces resting forearm vascular resistance (vasodilation) and rapidly normalizes baroreflex-mediated forearm vascular responses to simulated orthostasis (Figure 14).[11]

SUMMARY

Heart failure in both experimental and clinical settings is characterized by neurohormonal activation, a prominent component of which is sympathetic excitation. Impairment of normal modulating cardiopulmonary and arterial baroreflex mechanisms appears to be an important etiologic component of sympatho-excitation in heart failure. As has been previously shown in animal models, *acute* digitalis administration results in profound sympatho-inhibition, peripheral vasodilation, and normalization of baroreflex-mediated responses in patients with heart failure. Such effects, if maintained during long-term administration, also would be expected to improve cardiac function and perhaps the prognosis for these patients. The test of this hypothesis will require prospective, randomized, and placebo-controlled trials with large numbers of heart failure patients.

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DISCUSSION

Dr. Leier: I would like to touch briefly on digitalis and baroreceptor control in hypertension.

Dr. Ferguson: I think hypertension is associated with impairment of arterial baroreflex mechanisms in at least prehypertensive and mildly hypertensive patients. Dr. Mancia, has digitalis in your group been shown to potentiate arterial baroreflex control of heart rate?

Dr. Mancia: Yes, both in normotensive and hypertensive subjects. Baroreflex sensitivity was lower in hypertensive patients, but potentiation by digitalis was about the same in both groups.

Dr. Leier: Did you see an antihypertensive effect with digitalis?

Dr. Mancia: I do not think there was any effect on blood pressure (BP). We have done a lot of studies of the effects of antihypertensive agents on the baroreflex, particularly looking at BP control by the carotid sinus using the neck chamber technique. In fact, most of the drugs reset the reflex toward a lower BP level but do not harm baroreflex sensitivity substantially. This includes angiotensin-converting enzyme (ACE) inhibitors. In patients with hypertension, an ACE inhibitor will slightly increase baroreflex sensitivity in the portion of the stimulus–response curve that is below baseline, but reflex features more or less remain the same, except that they are always set to lower BP levels.

But the situation is completely different in congestive heart failure (CHF).

Dr. Gheorghiade: In assessing the effects of digitalis preparations, there may be a dissociation between the hemodynamic response and the neurohormonal response. For example, in a patient with an ejection fraction of 0.20 who has normal cardiac output and normal pulmonary capillary wedge pressure, digitalis will neither decrease wedge pressure nor increase cardiac output. However, activation of the neuroendocrine systems is often present[1] in a patient like this and may be attenuated by digitalis. Theoretically, digitalis preparations may blunt the excessive and possibly detrimental sympathetic outflow without an improvement in hemodynamics. In the past I have called patients who did not improve their hemodynamics in response to digoxin "nonresponders." They are "nonresponders" in terms of hemodynamic changes; however, at least theoretically, there may be a dissociation between hemodynamic and neuroendocrine beneficial effects from the drug.

Dr. Ferguson: I think that is possible. It is going to be very tough, I think, to establish that.

Dr. Mancia: We did a study[2] of the modulation of sympathetic nerve activity by phenylephrine and nitroglycerin. There is no doubt that the response to nitroprusside is more evidently impaired in subjects with CHF. You cannot really increase sympatho-excitatory response by giving nitroprusside, whereas you can have a reduction in sympatho-inhibitory responses with phenylephrine. In our experience, even considering mean arterial pressure as the stimulus, the response in patients with CHF was less than that of the control group with phenylephrine, but not as dramatically impaired as that with nitroprusside. So you can make the point that baseline values have importance here.

Dr. Ferguson: The fact that not all heart failure patients tolerate intravenous phenylephrine well may complicate the task of interpreting the data from such studies. The pulmonary vascular congestion induced by phenylephrine may activate other reflexes in some patients, and that may increase nerve activity at the time you are trying to reduce it by loading the arterial and cardiopulmonary afferents.

Dr. Mancia: It is interesting that even here we may have some differences among baroreceptor control, heart rate, and BP, because if you look at it the other way around, the bradycardiac response is the one that is more markedly impaired. The tachycardiac response is impaired, but it is less evident. When you look at sympathetic traffic, if anything, the opposite is true.

I think the evidence is very strong that the digitalis glycosides have a direct effect on the baroreflex, and this may be what is needed to improve reflex function in patients with heart failure. Other drugs—hydralazine, for example, which can increase cardiac output and stroke volume in certain patients—have no effect on the baroreflex.

Dr. Ferguson: I think you are right. The mechanistic studies by Wang et al[3] in a well-designed animal preparation suggest that we are probably looking at a membrane-acting action of digitalis. There may be other effects as well.

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Acute Hemodynamic Effects of Digoxin Alone or in Combination with Other Vasoactive Agents in Patients with Congestive Heart Failure

James E. Tisdale, PharmD, and Mihai Gheorghiade, MD

Although digitalis preparations have been in use for >200 years, it is only within the last 2 decades that the central hemodynamic and neurohumoral effects occurring over several hours following intravenous administration of digoxin have been investigated in patients with congestive heart failure (CHF). Although digoxin has been shown to stimulate myocardial contractility in tissue preparations, its positive inotropic activity does not consistently translate into improvements in hemodynamic measurements in humans. Digoxin given intravenously results in increased cardiac index and decreased heart rate, left ventricular filling pressure, and right atrial pressure, as well as in acute attenuation of neurohumoral abnormalities, in patients with chronic CHF who have abnormal baseline hemodynamic measurements. Unlike other drugs with positive inotropic activity, however, digoxin does not influence hemodynamics in normal volunteers or in CHF patients in whom hemodynamics have been normalized with other therapies. These differing effects may be related to the drug's diverse peripheral vascular effects in CHF patients in whom vasodilation may occur in comparison with those that occur in normal subjects in whom the peripheral vasoconstrictor effects may prevent the inotropic effects of the drug from being translated into an increase in cardiac output. The hemodynamic effects of digoxin in patients with chronic CHF due primarily to diastolic dysfunction have not been fully investigated. Intravenous digoxin produces hemodynamic effects in patients with CHF associated with acute myocardial infarction, but these changes are small compared with those resulting from the administration of dobutamine. Digoxin does not appear to influence hemodynamic measurements in patients with right ventricular dysfunction unless concomitant left ventricular failure is present. In patients with chronic left ventricular dysfunction, the hemodynamic effects of intravenous digoxin and vasodilators are enhanced when these agents are given in combination.

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Although digitalis glycosides have been in use for >200 years,[1] the pharmacologic effects of these agents are still not completely understood. During the 19th century, the primary actions of digitalis were believed to be slowing of the rate and improvement of the rhythm of the heart, and these agents were recommended primarily for use in patients with rapid and irregular pulse.[2] It was not until the early 20th century that digitalis was also considered to be useful in patients with congestive heart failure (CHF) who were in sinus rhythm.[3–6] Subsequently, Wiggers and Stimson[7] observed that digitalis increases development of intraventricular pressure at the initiation of systole. These initial findings regarding the positive inotropic effects of digitalis glycosides were confirmed in 1938 by Cattell and Gold,[8] who demonstrated that ouabain increases the force of contraction of electrically driven isolated papillary muscle. During the 1950s and 1960s, a series of studies established that the inotropic effects associated with digitalis occur in normal as well as in failing myocardium.[9–11] Only relatively recently has some agreement been reached regarding the cellular mechanism of action of the inotropic effect of digitalis,[12,13] namely, inhibition of the adenosine triphosphatase (ATPase)-dependent sodium–potassium pump in the sarcolemmal membrane of the cardiac myocyte.[14] This selective inhibition of this active-transport, monovalent cation pump ultimately results in increased availability of calcium

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to contractile proteins within myocardial cells, increasing the force of myocardial contraction.[15,16]

Although the effects of digitalis glycosides on the human heart have been extensively studied, investigations have focused primarily on the biochemical, cellular and electrophysiologic mechanisms by which these agents influence myocardial contractility.[11,17–20] However, improvements in indices of contractility resulting from acute digitalis administration often do not translate into significant changes in cardiac output or left ventricular filling pressure. A number of studies conducted in the 1940s, 1950s, and 1960s evaluated the central hemodynamic effects of digitalis preparations occurring within 2 hours following administration.[21–31] These studies suggested that the beneficial influence of digitalis on parameters such as cardiac output, left ventricular filling pressure and systemic vascular resistance occurs primarily in patients with abnormal baseline hemodynamic variables.[21,24,26,27,29,31,32] It has also been proposed that the clinical improvement associated with digitalis in CHF patients is due primarily to relief of circulatory congestion rather than to increases in myocardial contractility.[33]

Since modern advances in continuous hemodynamic monitoring have been realized only within the last 20 years, it was not until relatively recently that the hemodynamic effects of digoxin occurring over several hours following its administration were studied in patients with CHF due to systolic dysfunction. The purpose of this article is to review studies published during the last 2 decades that have investigated the acute hemodynamic effects of intravenous digoxin given alone or in combination with other vasoactive agents in patients with chronic CHF who are in sinus rhythm.

ACUTE HEMODYNAMIC EFFECTS OF DIGOXIN ALONE IN PATIENTS WITH CHRONIC HEART FAILURE

The hemodynamic effects of acute digoxin administration in patients at rest and during exercise have been evaluated by a number of investigators. Cohn and colleagues[34] studied the effects of 2 doses of intravenous digoxin 0.5 mg, separated by 2 hours, on central hemodynamic parameters at rest and during exercise in 8 patients with stable New York Heart Association (NYHA) functional class III or IV heart failure who were receiving maintenance diuretic therapy. Left ventricular ejection fraction was not assessed. Digoxin produced an increase in cardiac index in association with a decrease in systemic vascular resistance at rest in 4 patients. In the remaining 4 patients, however, digoxin administration resulted in reductions in cardiac index in association with increases in systemic vascular resistance (Figure 1). In 1 of these patients, this hemodynamic deterioration was related to the onset of ventricular arrhythmias. Each of the 3 remaining patients in whom cardiac index deterioration had occurred had substantially higher baseline cardiac index and lower pulmonary arterial wedge pressure (PAWP) values than those in whom digoxin increased cardiac index. This study demonstrated that intravenous digoxin administration does not elicit beneficial hemodynamic effects in all patients with severe CHF. However, since left ventricular ejection fractions were not determined, it is unclear as to whether this lack of efficiency was related to differences in type of heart failure (systolic vs diastolic dysfunction).

Gheorghiade et al[35] evaluated the hemodynamic effects of intravenous digoxin in 11 patients with NYHA class IV heart failure due to ischemic

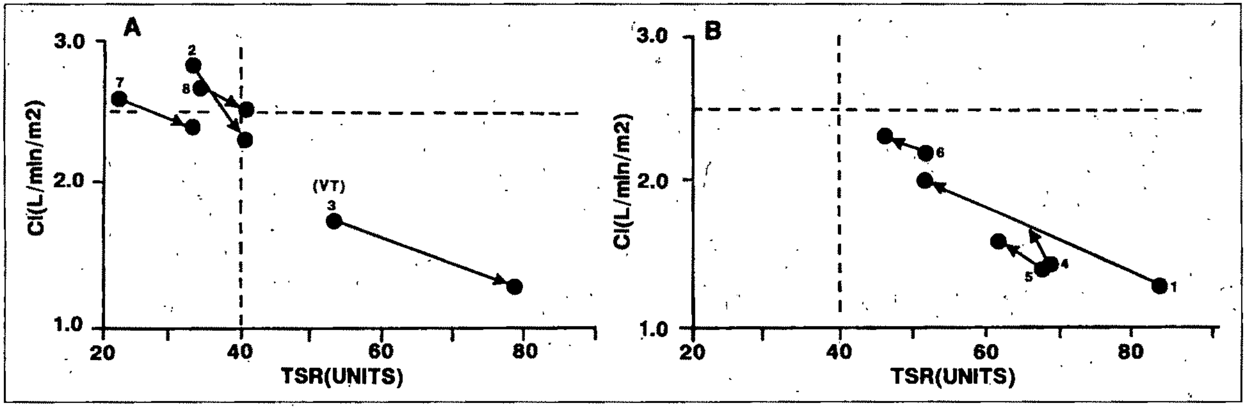

FIGURE 1. Transient changes in total systemic resistance (TSR) 30–60 minutes after digoxin administration in 8 cases were accompanied by alterations in cardiac index (CI). *A*, In 4 patients, an increase in TSR was accompanied by a reduction in CI; *B*, in the remaining 4 patients, an increase in CI was associated with a reduction in TSR. Of the 4 patients in whom TSR increased (*A*), 3 had normal systemic resistance prior to digoxin administration; although digoxin did not elevate TSR above the upper limit of normal (40 units), CI decreased. The remaining patient (3) developed runs of nonsustained ventricular tachycardia (VT) during this study. (From *Am J Cardiol.*[34])

TABLE I Peak Hemodynamic Response to Digoxin in 11 Patients

	Responders (n = 6)			Nonresponders (n = 5)		
	Control	Digoxin	p Value	Control	Digoxin	p Value
HR (beats/min)	107 ± 24	98 ± 29	0.05	85 ± 12	85 ± 13	NS
PAWP (mm Hg)	28 ± 5	18 ± 2	0.004	17 ± 5	17 ± 6	NS
CI (liters/min/m²)	2.1 ± 0.3	3.1 ± 0.02	0.02	3.1 ± 0.6	3.4 ± 0.6	NS
SVR (dynes · s · cm⁻⁵)	1,775 ± 317	1,229 ± 236	0.04	1,285 ± 282	1,332 ± 218	NS
EF (%) (n = 8)	20 ± 6	28 ± 6	0.03	28 ± 17	30 ± 20	NS

CI = cardiac index; EF = ejection fraction; HR = heart rate; NS = not significant; PAWP = pulmonary artery wedge pressure; SVR = systemic vascular resistance.
Adapted from *J Am Coll Cardiol.*[35]

or dilated cardiomyopathy. Mean left ventricular ejection fraction was 21 ± 13%. All patients in this study initially had overt heart failure that responded to therapy with maximal doses of diuretics and vasodilators over a period of 2–6 days. When a plateau in improvement in heart failure score was achieved, patients received 2 doses of intravenous digoxin 0.5 mg separated by 2 hours. Hemodynamic measurements were performed immediately prior to and every hour for 6 hours following administration of the first dose. Cardiac index and stroke work index increased following digoxin administration, while PAWP decreased. However, although mean data demonstrated improved hemodynamics in this group, only 6 of the 11 patients studied were considered responders (defined as those who experience a decrease in PAWP >5 mm Hg and an increase in cardiac index >0.5 liters/min/m² following dosing) (Table 1). No significant differences in age, etiology of heart failure, heart failure score, or left ventricular ejection fraction were found between patients who responded to digoxin and those who failed to respond. Responders, however, had significantly higher baseline PAWP values and lower cardiac index measurements than nonresponders (Figure 2).

Ribner and associates[36] investigated the hemodynamic and neurohumoral effects of digoxin in 11 patients with heart failure due to dilated cardiomyopathy. All but 1 patient in this study had NYHA class III heart failure, and all patients had left ventricular ejection fraction <35%. Central hemodynamic measurements were performed and blood samples obtained for the determination of plasma renin activity (PRA) and norepinephrine, epinephrine, and arginine vasopressin concentrations at rest and during submaximal exercise prior to and 6 hours following intra-atrial administration of digoxin 1 mg. Digoxin produced decreases in heart rate, PAWP, right atrial pressure, and pulmonary arterial diastolic pressure and increases in cardiac output, both at rest and during exercise (Table II). However, no changes in systemic vascular resistance occurred either at rest or during exercise. Plasma norepinephrine concentrations decreased at rest and during exercise, and these changes

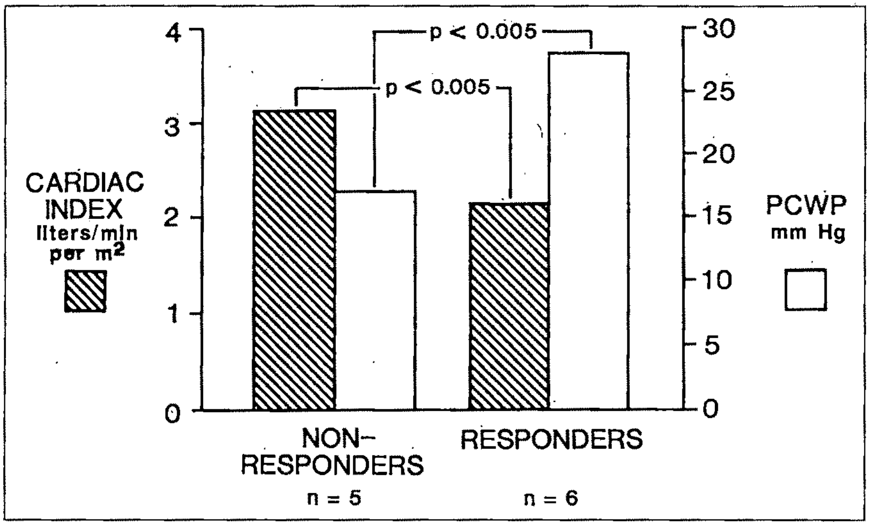

FIGURE 2. Baseline differences in cardiac index and pulmonary capillary wedge pressure (PCWP) between 5 nonresponders and 6 responders immediately prior to digoxin administration. (Reproduced with permission from *J Am Coll Cardiol.*[35])

TABLE II Hemodynamic and Hormonal Changes in Response to 1.0 mg Digoxin in 11 Patients with Dilated Cardiomyopathy

	Heart Rate (beats/min)	CO (liters/min)	PAWP (mm Hg)	Norepinephrine (pg/mL)	PRA (ng/mL/hr)	Aldosterone (pg/mL)
Rest (Sitting)						
Baseline	95 ± 3	3.3 ± 0.1	13 ± 2	755 ± 62	2.8 ± 0.8	274 ± 36
6 hours	90 ± 3*	3.7 ± 0.3*	9 ± 2*	544 ± 64*	1.9 ± 0.6*	208 ± 29*
Peak Exercise						
Baseline	115 ± 3	5 ± 0.2	20 ± 3	1,589 ± 225	5.2 ± 1.5	268 ± 25
6 hours	106 ± 3*	5.7 ± 3*	13 ± 4*	1,180 ± 229*	2.6 ± 0.9*	253 ± 45

*p <0.05 compared to baseline.
CO = cardiac output; PAWP = pulmonary artery wedge pressure; PRA = plasma renin activity.
Adapted from *Am J Cardiol.*[36]

correlated with increases in cardiac output. PRA also decreased at rest and during exercise.

Other investigators also have reported changes in neurohumoral activity following intravenous digoxin administration. Covit and colleagues[37] obtained blood samples for the determination of PRA and aldosterone concentrations after giving 0.5 mg digoxin intravenously to 6 patients with chronic NYHA class III or IV heart failure. PRA and aldosterone concentrations decreased and reached their nadir 3 hours after drug administration, returning to baseline values within 7 hours (Figure 3). This study provided further evidence that, in addition to modifying hemodynamic status, digoxin acutely attenuates the neurohumoral abnormalities associated with chronic heart failure.

Powell and associates[38] attempted to correlate the hemodynamic and electrophysiologic effects of digoxin with uptake of the drug by the myocardium. Digoxin 0.5 mg was administered intravenously to 14 patients undergoing cardiac catheterization for the investigation of acute chest pain. Hemodynamic measurements were performed intermittently for 30 minutes following dosing, and myocardial digoxin uptake was estimated by comparing drug concentrations in serial plasma samples obtained directly from the coronary sinus with those in plasma samples obtained from the femoral artery. As expected, digoxin did not influence cardiac index or left ventricular filling pressures, since baseline hemodynamic values were only mildly abnormal in these patients. However, digoxin did produce increases in mean arterial pressure and a positive inotropic effect, as demonstrated by an increase in mean left ventricular *dP/dt* (ratio of change of ventricular pressure to change in time). There was a trend toward a relationship between changes in *dP/dt* and estimated myocardial digoxin content. The effects of digoxin on myocardial contractility were preceded by its electrophysiologic effects (Figure 4).

Arnold et al[39] conducted a study to determine whether the acute hemodynamic effects of intravenous digoxin are sustained during chronic oral therapy. Central hemodynamic measurements were performed in 9 patients with NYHA class II or III heart failure during long-term oral digoxin therapy

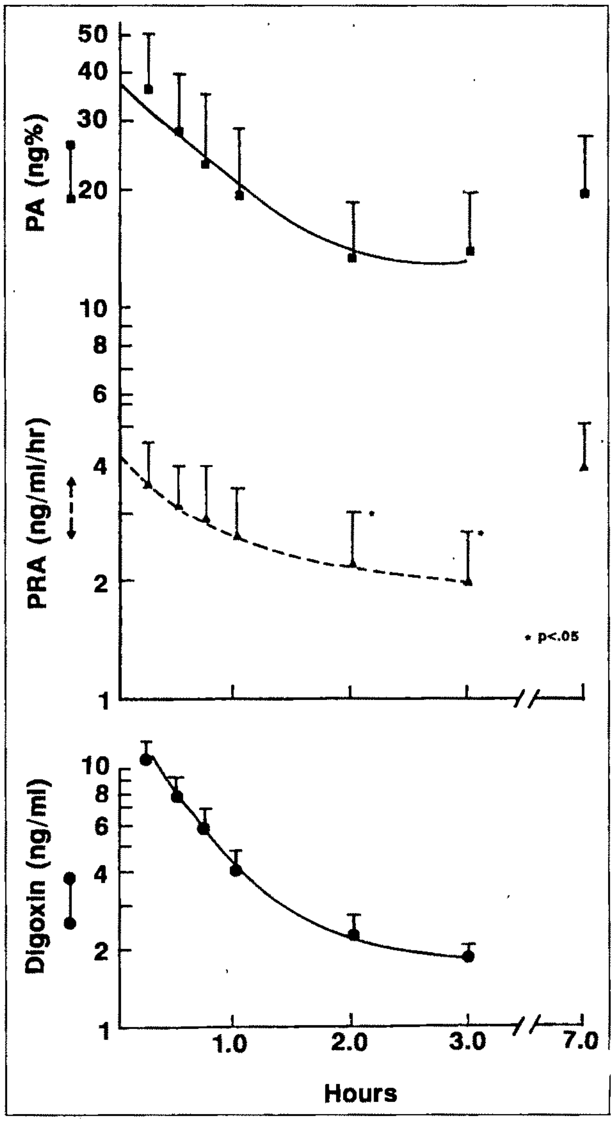

FIGURE 3. Plasma renin activity (PRA) and aldosterone concentration (PA) (mean ± SEM) in patients with chronic congestive heart failure after intravenous administration of 0.5 mg of digoxin. Serum digoxin concentrations are also provided. (Reproduced with permission from *Am J Med.*[37])

TABLE III Hemodynamic Data (Mean ± SD)

	Long-Term Oral Digoxin	Long-Term Oral Digoxin Plus Infusion	Digoxin Withdrawal	Digoxin Readministration (iv)	p Value
Rest					
Mean PCWP (mm Hg)	21 ± 77	19 ± 5.7	29 ± 9.5	22 ± 9.4	0.001
CI (liters/min/m^2)	2.4 ± 0.7	2.5 ± 0.6	2.1 ± 0.6	2.5 ± 0.5	0.025
Exercise					
Mean PCWP (mm Hg)	33 ± 7	31 ± 9	42 ± 5	35 ± 6	0.001
CI (liters/min/m^2)	3.5 ± 0.9	3.9 ± 1.4	3.1 ± 1.2	3.8 ± 1.1	0.05

CI = cardiac index; iv = intravenous; PCWP = pulmonary capillary wedge pressure.
Adapted with permission from *N Engl J Med.*[39]

(0.125–0.25 mg daily), 6–7 weeks following discontinuation of treatment, and 4–5 hours after readministration of digoxin intravenously. Mean serum digoxin concentration prior to entry into the study was 1.1. ± 0.4 ng/mL. The administration of an intravenous dose of digoxin (0.25–0.5 mg) to patients already receiving long-term oral digoxin therapy did not significantly enhance the hemodynamic response. Following withdrawal of oral digoxin therapy, 4 patients experienced marked clinical deterioration, requiring hospitalization within 1 month. In all patients, hemodynamic deterioration occurred at rest and during exercise after withdrawal of therapy, as reflected by significant decreases in cardiac index and left ventricular ejection fraction and a significant increase in PAWP (Table III). Following readministration of intravenous digoxin, resting and exercise hemodynamic values were almost identical to those measured prior to withdrawal of oral therapy. The results of this study suggest that the acute hemodynamic effects of intravenous digoxin are sustained during long-term oral therapy.

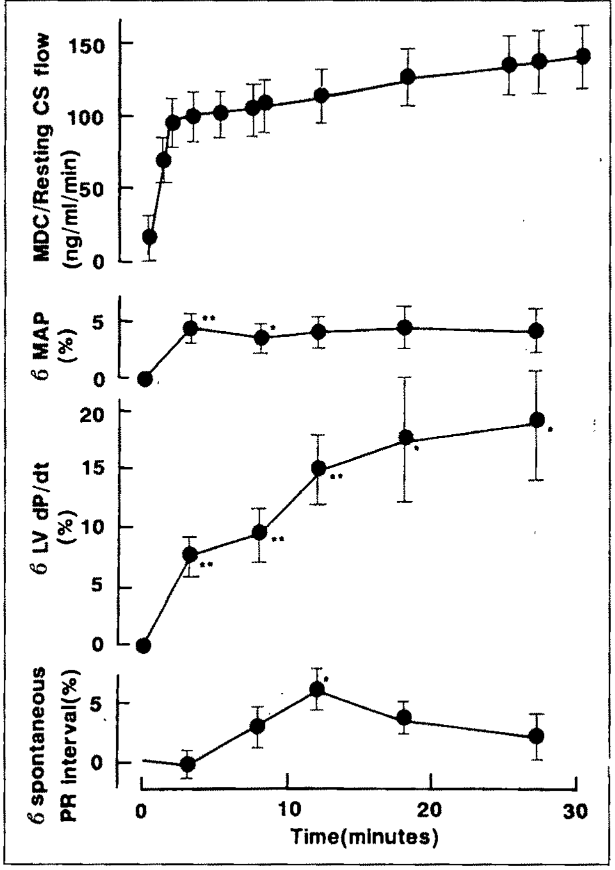

FIGURE 4. Time course of myocardial digoxin uptake expressed as myocardial digoxin content (MDC) relative to baseline coronary sinus (CS) blood flow, percent change in mean arterial pressure (ΔMAP), percent change in left ventricular peak positive *dP/dt* (ΔLV *dP/dt*) and change in spontaneous PR interval (Δ spontaneous PR interval) for 30 minutes after intravenous bolus injection of digoxin. *$p < 0.05$; **$p < 0.01$. (Reproduced with permission from *J Am Coll Cardiol.*[38])

Griffiths and colleagues[40] also provided evidence that chronic oral digoxin treatment continues to exert a positive inotropic effect over time. The investigators studied 11 patients with NYHA class I to III heart failure who had been receiving oral digoxin for ≥ 10 months. M-mode echocardiograms were performed and systolic time intervals measured prior to, and 6 weeks following, discontinuation of digoxin. Significant decreases in left ventricular internal cavity dimensions during both systole and diastole occurred after withdrawal of therapy, as did significant decreases in velocity of circumferential myocardial fiber shortening and significant increases in QS_2 and ejection time. Although this study may be criticized for its design and use of noninvasive measurements, the result provides additional evidence of digoxin's sustained positive inotropic effects during chronic oral treatment.

Although data regarding the hemodynamic effects of digoxin in patients with CHF due to systolic dysfunction are available, the drug's hemodynamic effects in patients with heart failure primarily due to diastolic dysfunction are unknown.[41] In theory, by increasing intracellular calcium concentrations, digitalis glycosides might be expected to elicit adverse hemodynamic effects in such patients by impairing left ventricular relaxation.[41] However, animal studies[42,43] have shown that neither digoxin nor ouabain influences ventricular relaxation. A recent study[44] suggested that in patients with coronary artery disease, preserved left ventricular function, and no evidence of prior myocardial infarction, acute administration of K-strophanthidin appears to increase myocardial contractility and impair ventricular relaxation. Although limited data suggest that digoxin does not improve clinical symptoms in patients with heart failure who have preserved left ventricular function,[45] the hemodynamic effects of digitalis preparations in patients with diastolic dysfunction, preserved systolic function, and clinical CHF remain to be investigated.

Based on these data, it appears that, in patients in sinus rhythm with chronic CHF due to systolic dysfunction, intravenous digoxin administration results in beneficial hemodynamic effects and attenuation of neurohumoral abnormalities in those with abnormal baseline hemodynamic values but, unlike other agents with positive inotropic activity,[46] exerts little influence on hemodynamics in those with minimal abnormalities in baseline hemodynamic parameters. This variable response to digoxin among patients with differing degrees of hemodynamic derangement may be related to the drug's peripheral effects, which may prevent digoxin-induced increases in myocardial contractility from being translated into increases in cardiac output.[47] In normal subjects, digitalis preparations have been shown to increase systemic vascular resistance[11,48] and cause coronary vasoconstriction.[49] These effects may be related to a local direct action on vascular smooth muscle[48] or to a neurogenically mediated vasoconstriction.[50–54] In addition, digitalis may cause vasoconstriction by activating angiotensin II.[55,56] It should be noted, however, that the peripheral vasoconstricting properties of digitalis are transient and occur only after rapid intravenous administration.[49] In contrast, peripheral vasoconstriction following digitalis therapy has not been observed in patients with chronic CHF. Heart failure is associated with decreased baroreceptor sensitivity[57] and increased neurosympathetic outflow.[58] Since digitalis may improve abnormal baroreceptor responsiveness[59] and decrease sympathetic outflow,[60] the local vasoconstricting effect of the drug may be inhibited. In fact, maximal vasoconstriction may already be present in patients with severe heart failure before they receive digitalis; thus, the positive inotropic effects of the drug may be translated into increases in cardiac output. Indeed, peripheral vasodilation has been observed in response to digitalis in patients with heart failure.[29]

ACUTE HEMODYNAMIC EFFECTS OF DIGOXIN IN PATIENTS WITH HEART FAILURE ASSOCIATED WITH MYOCARDIAL INFARCTION

Although digitalis glycosides have been given to patients with acute myocardial infarction since the early 1900s,[61] use of these preparations in this patient population remains controversial. Although digitalis may be beneficial in patients with acute myocardial infarction who are experiencing atrial fibrillation, a number of studies[62–66] have failed to demonstrate substantial beneficial hemodynamic effects resulting from administration of digitalis glycosides in patients with mild heart failure and sinus rhythm during the acute phase of myocardial infarction. In 1 study, only 4 of 10 patients with mild heart failure following myocardial infarction experienced a demonstrable improvement in left ventricular function.[63] Goldstein et al[64] reported no major effect of intravenous digoxin on PAWP or systemic vascular resistance in patients with heart failure within 24 hours after acute myocardial infarction. However, it should be noted that it is unclear whether patients in this study developed heart failure due to systolic or diastolic dysfunction. Digoxin did produce significant increases in cardiac index and stroke work index, but the magnitude of these changes was small in comparison with the changes obtained using dobutamine.

In contrast, some studies have reported hemodynamic improvements associated with digoxin use in patients with heart failure after acute myocardial infarction. Lipp and associates[67] observed significant improvements in systemic arterial pressure and left ventricular stroke work index in patients with heart failure following myocardial infarction, but reported no significant hemodynamic benefits in patients without heart failure. Similar benefits have been reported using ouabain in patients with heart failure during the postmyocardial infarction period.[68] Marchionni et al[66] evaluated the hemodynamic effects of intravenous digoxin within 12 hours of the onset of acute myocardial infarction in 40 patients who were each assigned to 1 of 4 hemodynamic subsets based on the relation between PAWP and left ventricular stroke work index. Left ventricular ejection fractions were not determined. Hemodynamic subsets were defined as follows: subset 1: normal PAWP (≤ 15 mm Hg), normal left ventricular stroke work index (≥ 35 g-m/m^2); subset 2: elevated PAWP, normal left ventricular stroke work index; subset 3: normal PAWP, reduced left ventricular stroke work index (<35 g-m/m^2); subset 4: elevated PAWP and moderately reduced left ventricular stroke work index (16–34 g-m/m^2). Within each hemodynamic subset, patients were randomized to receive intravenous digoxin or placebo. In patients in subsets 1 and 2, the drug exerted no significant sustained hemodynamic effects. However, digoxin increased cardiac index in patients in subsets 3 and 4, and decreased right atrial pressure and PAWP in subset 4. Although it is unknown whether these patients were experiencing systolic or diastolic dysfunction, these data suggest that intravenous digoxin produces significant hemodynamic improvement following myocardial infarction only in patients with left ventricular failure of at least moderate severity. Limited data suggest that the hemodynamic improvements resulting from digoxin administration in these patients appear to be small in comparison with those obtained using dobutamine.[64]

It is possible that the demonstrated hemodynamic effects of dobutamine in patients with heart failure associated with myocardial infarction are related to this drug's ability to enhance contractility in stunned myocardium.[69] Although digitalis has been shown to stimulate contractility in ischemic myocardium,[70–72] in patients with coronary artery disease it has produced substantially smaller improvements in velocity of circumferential fiber shortening in segments of myocardium that were contracting abnormally due to myocardial ischemia than in normal segments.[73] The response of myocardial tissue to digitalis glycosides appears to depend on the relative quantity of viable myocardial tissue versus the quantity of ischemic or infarcted myocardium.[74] The relatively limited hemodynamic effects of digoxin in patients with heart failure due to acute myocardial infarction may be a consequence of the failure of ischemic and necrotic myocardial tissue to respond to the drug.[63] The action of digoxin in stunned or hibernating myocardium following acute myocardial infarction remains to be investigated. It should be noted, however, that heart failure associated with acute myocardial infarction may be due to a combination of systolic and diastolic dysfunction and that one or the other may predominate. It is therefore difficult to evaluate fully the effects of digoxin in this patient population without assessing the mechanism of heart failure. Digoxin may be of some benefit in patients with low left ventricular ejection fractions following acute myocardial infarction.

In summary, digoxin administration appears to result in relatively little hemodynamic improvement in patients with normal hemodynamics or mild hemodynamic abnormalities following acute myocardial infarction. However, in patients with elevated PAWP or decreased cardiac output following myocardial infarction, digoxin may significantly influence hemodynamic measurements. The hemodynamic benefits of the drug appear to be achieved in these patients without increasing the risk of the immediate postmyocardial infarction arrhythmias[75] and, although some data are contradictory,[76] without influencing infarct size. In fact, Morrison et al[77] found that in patients with acute myocardial infarction complicated by CHF, intravenous digoxin increased the ejection fraction from 29% to 33% (no changes in ejection fraction were noted in the control group) with no apparent effect on infarct size assessed by the thallium-201 perfusion scan or on the abnormal contractile segments assessed by radionuclide ventriculography.

HEMODYNAMIC EFFECTS OF DIGOXIN IN PATIENTS WITH RIGHT VENTRICULAR DYSFUNCTION

The hemodynamic effects of digoxin in patients with isolated right ventricular dysfunction have not been well studied. The only available data regarding the drug's acute hemodynamic effects in this patient population were published by Aubier et al.[78] The effect of digoxin administration on hemodynamic variables was determined in 8 patients with chronic obstructive pulmonary disease who were admitted to an intensive care unit for management of acute respiratory failure. All patients in this study had clinical signs of right heart failure and electrocardiographic signs of right ventricular hypertrophy. Cardiac index, pulmonary artery pressure, and PAWP were measured prior to, and 45 and 90 minutes following, intravenous administration of digoxin 0.02 mg/kg. Digoxin produced no significant changes in any measured hemodynamic parameter. However, baseline cardiac index and PAWP measurements were normal in all patients; only baseline pulmonary artery pressures were elevated in the study population. Digoxin augmented diaphragmatic contractility, which may be an important effect of this drug in patients with respiratory failure.

Mathur and colleagues[79] investigated the effects of digoxin administration on right and left ventricular ejection fractions in 15 patients with severe chronic airway obstruction and evidence of right ventricular dysfunction. In this double-blind study,

TABLE IV Peak Acute Hemodynamic Effects of Digoxin, Nifedipine, and Their Combinations in 12 Patients With Heart Failure

	Control	Nifedipine	Control	Digoxin	Digoxin + Nifedipine
LVFP (mm Hg)	19 ± 8	16 ± 1*	18 ± 8	14 ± 5*	12 ± 4*
CI (liters/min/m^2)	2.2 ± 0.5	2.6 ± 0.5*	2.2 ± 0.5	2.4 ± 0.4*	2.9 ± 0.4*
SWI (g · m/m^2)	30 ± 11	33 ± 10	33 ± 10	38 ± 11*	41 ± 8*

*$p < 0.05$.
CI = cardiac index; LVFP = left ventricular filling pressure; SWI = stroke work index.
Reproduced with permission from *Am Heart J.*[81]

patients were randomized to receive digoxin 0.25 mg orally or placebo daily for 8 weeks, and then crossed over to the alternate therapy. Radionuclide angiography was performed prior to, and at 8 and 16 weeks after beginning, the study. Baseline right ventricular ejection fractions were abnormal in all patients, whereas baseline left ventricular ejection fractions were abnormal in only 4 patients. Following 8 weeks of oral digoxin therapy, left ventricular ejection fraction increased in the 4 patients with low baseline values. Mean right ventricular ejection fraction did not change. However, improvements in right ventricular ejection fraction occurred in the 4 patients with abnormal baseline left ventricular ejection fraction; no patient with normal baseline left ventricular ejection fraction experienced an increase in right ventricular injection fraction. Brown and associates[80] evaluated the effects of digoxin on right ventricular function in 12 patients with severe chronic airflow obstruction. While 9 of these patients had electrocardiographic evidence of right axis deviation and/or signs of right ventricular hypertrophy, only 1 patient had a clinical history of right ventricular failure. Patients were randomized in a double-blind fashion to receive digoxin 0.25 mg orally or placebo daily for 2 weeks, and then crossed over to the alternate therapy. Radionuclide angiography was performed at rest and during exercise prior to and at the end of 2 weeks of therapy. Oral digoxin did not significantly influence mean right ventricular ejection fraction at rest or during exercise. In this study, however, whereas 8 of the 12 patients studied had abnormal baseline right ventricular ejection fractions, only 2 had abnormal baseline left ventricular ejection fractions. The effect of digoxin on right ventricular ejection fraction in the 2 patients with abnormal baseline left ventricular ejection fraction was not reported.

Based on these limited data, digoxin does not appear to influence hemodynamic measurements in patients with right ventricular dysfunction unless concomitant left ventricular dysfunction is present.

HEMODYNAMIC EFFECTS OF DIGOXIN IN COMBINATION WITH VASODILATORS OR POSITIVE INOTROPIC AGENTS

Several investigators have studied the hemodynamic effects of digoxin given in combination with various vasoactive agents in patients with heart failure. Cantelli and colleagues[81] compared the acute hemodynamic effects of intravenous digoxin and sublingual nifedipine administered alone and in combination in 12 patients with chronic NYHA class II to IV heart failure. Seven patients in this study had ischemic cardiomyopathy, and 5 had idiopathic dilated cardiomyopathy. Four patients had mitral regurgitation. Hemodynamic parameters were measured prior to and 30, 60, and 120 minutes following administration of nifedipine 10 mg sublingually. When hemodynamic measurements returned to baseline levels (at least 6 hours post dose), patients received digoxin 0.01 mg/kg intravenously, and hemodynamic measurements were repeated at 30, 60, and 90 minutes. At this time, an additional dose of nifedipine 10 mg was administered sublingually and hemodynamics were measured at 30, 60, and 120 minutes. The combination of digoxin and nifedipine resulted in an improvement in cardiac performance greater than that resulting from the administration of either agent alone. Given separately, digoxin and nifedipine each decreased left ventricular filling pressure and increased cardiac index (Table IV). There was no significant difference in hemodynamic response between patients with ischemic or idiopathic dilated cardiomyopathy. The greatest hemodynamic improvement associated with either drug occurred in patients with mitral regurgitation.

The hemodynamic effects of digoxin and hydralazine given alone and in combination were evaluated by Ribner and associates[82] in 14 patients with chronic NYHA class II to IV heart failure, all of whom had left ventricular ejection fraction $<35\%$, cardiac index <2.5 liters/min/m^2, and PAWP >12 mm Hg. Hemodynamic parameters were measured at rest and during exercise prior to and 30 minutes following intravenous administration of hydrala-

TABLE V Peak Acute Hemodynamic Effects of Digoxin, Hydralazine, and Their Combination in 14 Patients With Heart Failure

	Control	Hydralazine	Control	Digoxin	Digoxin + Hydralazine
PCWP (mm Hg)					
Rest	14 ± 3	10 ± 2*	14 ± 2	10 ± 2*	10 ± 2*
Exercise	22 ± 4	16 ± 1*	20 ± 3	13 ± 4*	10 ± 3*
CO (liters/min)					
Rest	3.1 ± 0.1	4 ± 2*	3.1 ± 0.2*	3.5 ± 0.2*	4.5 ± 0.2*
Exercise	5 ± 0.2	5.8 ± 0.4*	5.0 ± 0.3	5.5 ± 0.2*	6.8 ± 0.3*

*$p < 0.05$ compared with baseline.
CO = cardiac output; PCWP = pulmonary capillary wedge pressure.
Adapted from *Am Heart J.*[82]

TABLE VI Peak Hemodynamic Effects of Dobutamine or Digoxin in 7 Class IV Congestive Heart Failure Patients

	Baseline	Dobutamine	Baseline	Digoxin
CI (liters/min/m^2)	2.3 ± 0.8	3.2 ± 0.8	2.1 ± 0.7	3 ± 0.7
PAWP (mm Hg)	25 ± 6	15 ± 5	23 ± 6	15 ± 5
SVR (dynes · s · cm^{-5})	2,557 ± 630	1,629 ± 584	2,542 ± 540	1,793 ± 378

CI = cardiac index; PAWP = pulmonary artery wedge pressure; SVR = systemic vascular resistance.
Adapted from *Int J Clin Pharmacol Ther Toxicol.*[83]

zine 0.15 mg/kg. The next day, hemodynamic measurements were repeated at baseline and 5 and 6 hours following intravenous administration of digoxin 1.0 mg. Patients then received another intravenous dose of hydralazine 0.15 mg/kg, and hemodynamic measurements were obtained 30 minutes later. Administration of either agent alone produced increases in cardiac output and decreases in PAWP and right atrial pressure. Systemic vascular resistance and mean arterial pressure decreased following therapy with hydralazine alone, whereas mean arterial pressure increased following digoxin administration. Both drugs produced similar reductions in left and right ventricular filling pressures at rest and during exercise. Combination therapy resulted in greater increases in cardiac output and stroke volume at rest and during exercise than were achieved with either agent alone (Table V). Combination therapy did not produce additive effects on PAWP. This study provides further evidence that the hemodynamic effects of digoxin are augmented by concomitant vasodilator therapy.

Bonelli and Jancuska[83] studied the hemodynamic effects of digoxin and dobutamine administered alone and in combination in 7 patients with NYHA class IV heart failure due to dilated cardiomyopathy. Hemodynamic measurements were performed at baseline, 30 minutes after initiation of an intravenous infusion of dobutamine 7.5 μg/kg/min, and 30 minutes following its discontinuation. Patients then received digoxin 12.5 μg/kg intravenously, and hemodynamic measurements were performed 15, 30, 60, and 120 minutes later. An infusion of dobutamine 7.5 μg/kg/min was again initiated and hemodynamic variables were obtained 30 minutes later and again 30 minutes after the infusion was discontinued. Administration of either dobutamine or digoxin alone resulted in increases in cardiac index and decreases in PAWP and systemic vascular resistance (Table VI). Interestingly, and in contrast to data obtained in patients with heart failure during acute myocardial infarction,[64] increases in stroke volume index and stroke work index were higher following the administration of digoxin than those measured during therapy with dobutamine. Surprisingly, the combination of digoxin and dobutamine resulted in a modest decrease in PAWP but no additional increase in cardiac index. Heart rate–blood pressure index (double product) increased during dobutamine administration and decreased following digoxin administration. Double product during combination therapy was less than that measured during dobutamine administration but greater than that following digoxin therapy. This study demonstrated no advantage to the combination of digoxin and dobutamine, but did provide evidence that intravenous digoxin administration may result in hemodynamic benefits that are comparable with those of dobutamine in patients with severe heart failure due to systolic dysfunction.

Gheorghiade et al[84] studied the hemodynamic and neurohumoral effects of intravenous digoxin and captopril given alone and in combination to 16 patients with NYHA class III or IV heart failure due to ischemic or idiopathic dilated cardiomyopathy. Hemodynamic parameters were measured in all patients at rest and during exercise prior to drug administration. In 1 group of 9 patients, hemodynamic measurements were then performed 5–10 minutes after each of a series of intravenous bolus doses (1, 2, 4, and 8 mg) of captopril, and then serially for up to 8 hours following initiation of a continuous intravenous infusion of captopril 6 mg/hr. Digoxin 1 mg was administered intravenously 2 hours following initiation of the captopril infusion (Figure 5). In the other group of 7 patients, intravenous digoxin was given first, hemodynamic variables were measured and captopril therapy was initiated 3 hours later (Figure 6). Blood samples for the determination of plasma norepinephrine and aldosterone concentrations and PRA were obtained 2 and 6 hours after the first drug intervention in both groups. At rest, both captopril and digoxin given separately decreased PAWP and systemic vascular resistance, and digoxin alone increased cardiac index and stroke work index. During exercise, captopril decreased PAWP and increased cardiac index, whereas digoxin increased stroke work index and decreased PAWP. Given in combination, captopril and digoxin produced greater increases in cardiac index and stroke work index and greater decreases in PAWP and systemic vascular resistance than were achieved with either agent alone. In addition, only combination therapy improved exercise tolerance in this group of patients. Digoxin given alone and in combination with captopril resulted in decreases in plasma norepinephrine concentrations (Figure 7), which correlated with increases in stroke work index. The combination decreased plasma aldosterone concentrations. These acute neurohumoral effects of digoxin and captopril have been shown to persist during long-term therapy with either of these agents.[85]

Raabe[86] compared the hemodynamic effects of the combination of digoxin and sodium nitroprusside with those of nitroprusside alone in 11 patients in Killip class II or III CHF complicating acute myocardial infarction. Sodium nitroprusside therapy was initiated at a continuous infusion rate of 50 μg/min, which was increased by 17 μg/min every 10 minutes to achieve mean arterial pressure <70 mm Hg or PAWP <16 mm Hg. Hemodynamic measurements were performed 30 minutes after the infusion rate was stabilized. Digoxin 0.5 mg was then administered intravenously, and hemodynamic parameters were measured 30, 60, and 90 minutes later. Given alone, sodium nitroprusside

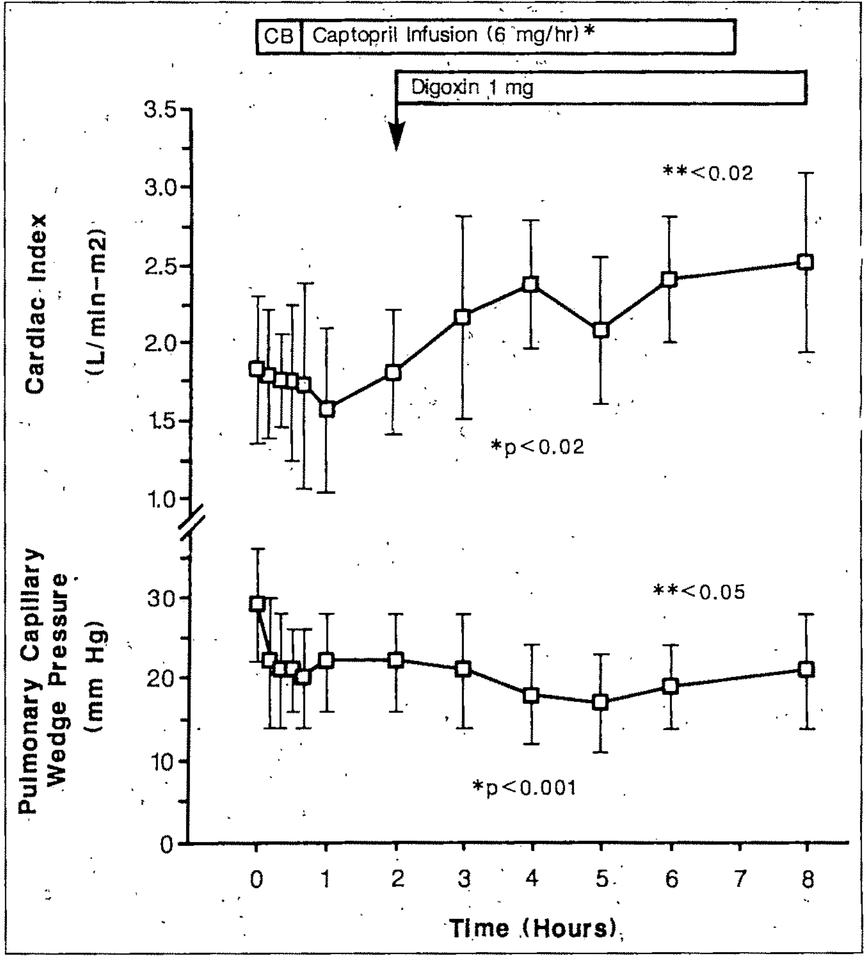

FIGURE 5. Serial changes in cardiac index and pulmonary capillary wedge pressure in group 1 (9 patients given captopril before digoxin).* Analysis of variance for repeated measurements over time in response to the combination of captopril and digoxin. **Comparison of the sum of mean hemodynamic values in each patient following administration of captopril bolus injections (CB) and continuous infusion compared with the sum of all mean values obtained after adding digoxin to captopril therapy. (Reproduced with permission from *J Am Coll Cardiol*.[84])

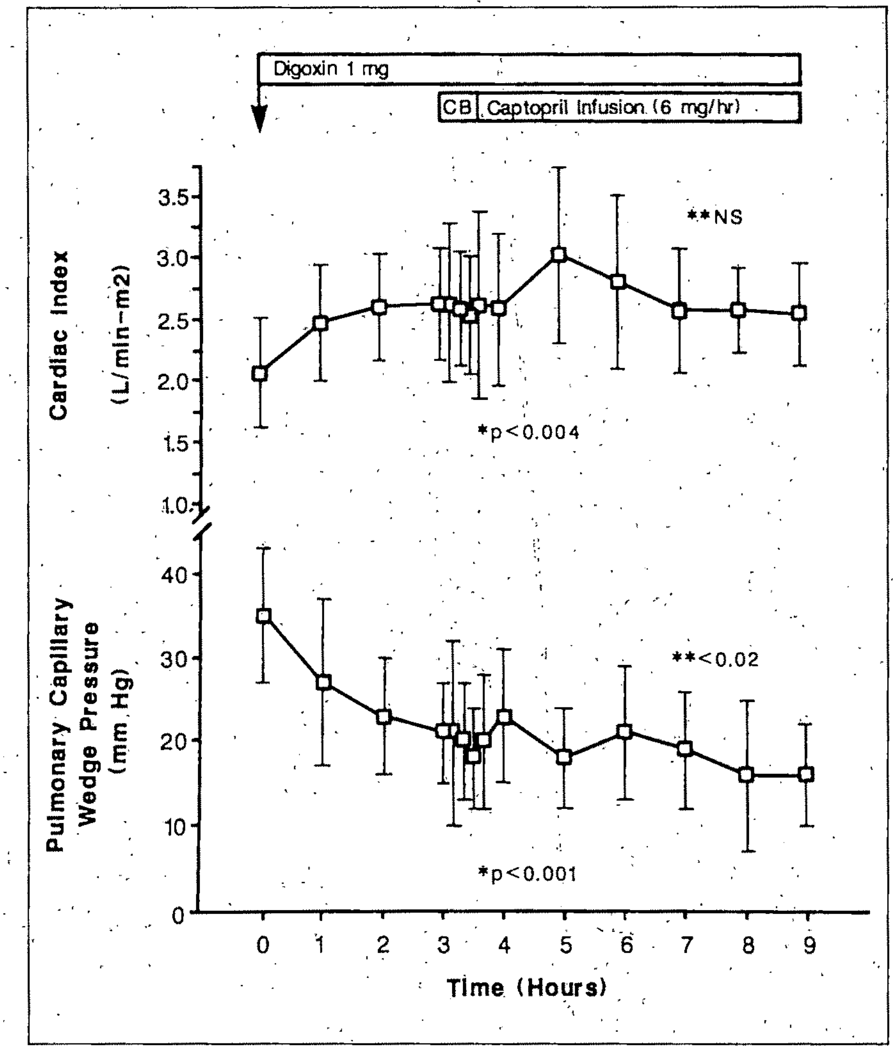

FIGURE 6. Serial changes in cardiac index and pulmonary capillary wedge pressure in group 2 (7 patients given digoxin before captopril).* Analysis of variance for repeated measurements over time. Comparison of the sum of mean hemodynamic values in each patient following digoxin administration compared with the sum of all mean values obtained after adding bolus injections (CB) and a continuous infusion of captopril. (Reproduced with permission from *J Am Coll Cardiol*.[84])**

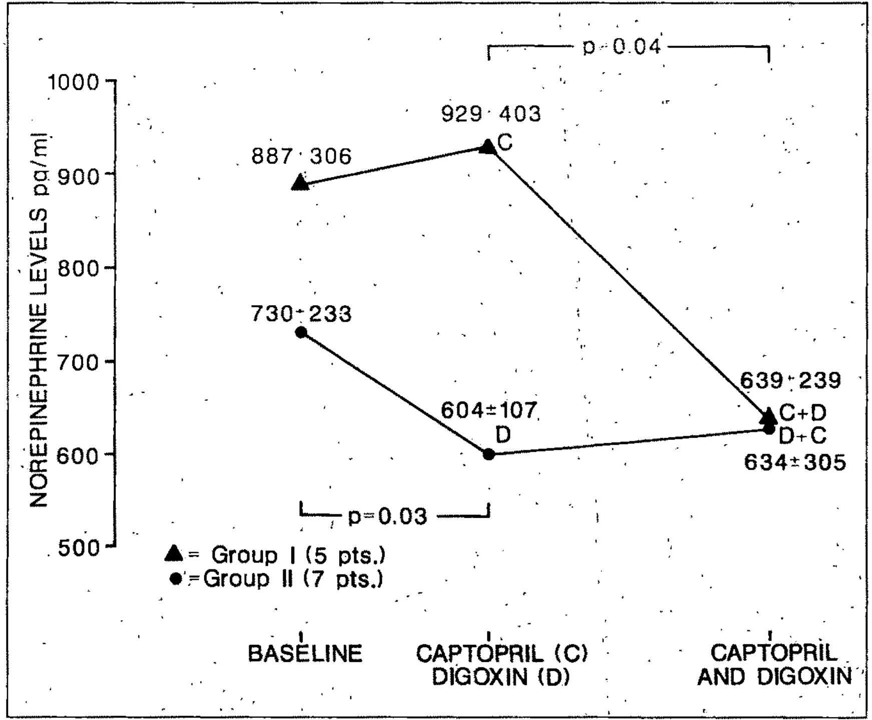

FIGURE 7. Plasma norepinephrine concentration changes in 12 patients in response to administration of captopril (C), digoxin (D), and the 2 agents combined (C + D). (Reproduced with permission from *J Am Coll Cardiol*.[84])

increased cardiac index and decreased PAWP, mean arterial pressure and systemic vascular resistance. The addition of digoxin resulted in an increase in stroke work index and an even greater increase in cardiac index and greater decrease in systemic vascular resistance than were obtained using sodium nitroprusside alone. Digoxin did not enhance the effects on PAWP already normalized with nitroprusside.

In summary, the effects of digoxin and vasodilators on cardiac index and, in some cases, PAWP and systemic vascular resistance are enhanced when those agents are used in combination in patients with chronic left ventricular dysfunction. Limited data suggest that combining digoxin and dobutamine does not enhance the hemodynamic effects of these agents.

CONCLUSION

Intravenous digoxin administration results in increased cardiac index and decreased heart rate, PAWP and right atrial pressure in chronic CHF patients with abnormal baseline hemodynamic values, and these hemodynamic benefits appear to be sustained during long-term oral digoxin therapy. In addition, neurohumoral abnormalities associated with CHF are attenuated following intravenous digoxin administration. In contrast, chronic CHF patients with normal baseline hemodynamic parameters or in whom hemodynamics have been normalized with diuretics or vasodilators may experience little improvement following intravenous digoxin administration. The hemodynamic effects of digoxin in patients with chronic heart failure due primarily to diastolic dysfunction remain unknown. Although digoxin may produce hemodynamic improvement in patients with moderate-to-severe heart failure following myocardial infarction, these benefits are relatively small compared with those obtained using dobutamine. However, in patients with chronic severe heart failure, the acute hemodynamic effects of intravenous digoxin are comparable to those of dobutamine. Digoxin has not produced substantial hemodynamic improvement in patients with right ventricular dysfunction unless concomitant left ventricular dysfunction is present. In patients with chronic left ventricular dysfunction, the hemodynamic effects of intravenous digoxin and vasodilators are enhanced when these agents are used in combination. It must be pointed out that, although hemodynamic response to therapy has been identified as an important predictor of survival in patients with cardiomyopathy who have left ventricular ejection fraction $<20\%$,[87] it remains unknown whether the hemodynamic improvements related to digoxin therapy are translated into clinical benefits or prolonged survival.

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Review of Randomized Trials of Digoxin Therapy in Patients with Chronic Heart Failure

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Although digitalis glycosides were introduced in the treatment of cardiac maladies >200 years ago, controversy persists regarding the precise role of digoxin in any multidrug approach to the treatment of congestive heart failure (CHF). Despite its widespread use for more than 2 centuries, only recently have double-blind, randomized, placebo-controlled trials of digoxin therapy been conducted in patients with moderate CHF and sinus rhythm. These trials demonstrate that digoxin is superior to placebo in improving left ventricular (LV) ejection fraction, increasing exercise capacity, and preventing CHF worsening. Digoxin produces benefits similar to those seen with angiotensin converting enzyme (ACE) inhibitors with regard to clinical compensation and improvement in LV function. However, improved survival is demonstrated only in response to ACE inhibitors. The recently completed RADIANCE study addresses the value of combining digoxin with ACE inhibitor therapy in patients with mild-to-moderate CHF. Because increased mortality has been reported with the newer oral inotropic agents, it currently appears that digoxin is the only oral inotropic agent useful in clinical practice in the treatment of CHF. However, the effects of digoxin on mortality in patients with CHF remain unknown. In the large, double-blind, randomized trial conducted by the National Heart, Lung, and Blood Institute, the effects of digoxin on mortality in patients with CHF and already being treated with ACE inhibitors are currently being evaluated.

Presently, based on the results of placebo-controlled studies, it appears that digoxin, alone or in combination with ACE inhibitors, is beneficial in patients with any signs or symptoms of CHF due to systolic LV dysfunction.

(Am J Cardiol 1992;69:48G–63G)

For >130 years after the first description by Withering[1] of the use of a digitalis preparation in the management of patients with dropsy, digitalis preparations were used primarily for the treatment of edema in the presence of rapid and irregular pulse. In the 1920s, based on the work of Christian,[2,3] Luten,[4] and Marvin,[5] evidence was presented suggesting that the drug was equally as effective in congestive heart failure (CHF) and sinus rhythm as in atrial fibrillation. This was further supported by Gavey and Parkinson,[6] who reported that digitalis produced similar but modest responses in patients whether they were in atrial fibrillation or in sinus rhythm. However, it was suggested that the beneficial effects were related to the peripheral vascular effect of digitalis and not related to its inotropic effects.[7] The belief that digitalis was a highly effective drug in the treatment of CHF and sinus rhythm was reinforced by the emergence of hemodynamic studies in the 1940s.[8,9] Rader et al[10] suggested that inotropic cardiac stimulation was not required for relief of symptoms in most cases of CHF, since amelioration of the congestive symptoms with either digitalis or diuretics was associated with clinical improvement without significant changes in intracardiac pressure or cardiac output.

In 1969 Starr and Luchi[11] conducted the first blinded study in elderly women who were in sinus rhythm. Neither patients nor investigators could distinguish differences in symptoms between digitoxin treatment and control periods after 1 month of therapy. Johnston and McDevitt[12] concluded that digoxin can be discontinued in many patients with a history of CHF who were in sinus rhythm without adverse effects. However, in their study, no objective hemodynamic or exercise parameters were evaluated, and indications for the initial digitalization in the patient cohort were not described. In addition, 60% had a subtherapeutic digoxin serum concentration in the prewithdrawal period. Among the 40% of patients with therapeutic serum concentration (0.8–2 ng/mL), 32% (7 of 22 patients) deteriorated when digoxin was discontinued. Dall[13] and Krakauer and Petersen[14] showed

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that digoxin therapy could safely be discontinued in 75% of geriatric outpatients receiving the drug. Hull and Mackintosh[15] also reported that digoxin withdrawal in patients with sinus rhythm did not produce any changes in cardiovascular signs or symptoms.

Similar observations were made by McHaffie et al[16] in patients treated first with diuretics. In these patients, after the signs of congestion were eliminated by the use of diuretics, no evidence of symptomatic improvement or enhanced exercise tolerance could be detected when digitalis was added to their therapeutic regimen.

Fonrose et al[17] stopped digitalis therapy in a group of patients taking a digitalis preparation for at least 1 year: 50% required digitalis to be prescribed again within 3–21 days after its discontinuation. The other patients were successfully maintained without the glycoside for periods of 4 months.

Only in the last 2 decades have randomized, placebo-controlled studies been undertaken to examine critically the efficacy of long-term maintenance digoxin therapy in the treatment of CHF. With the advent of potent diuretics and the demonstrated benefit of angiotensin converting enzyme (ACE) inhibitors, the value of digoxin in a multidrug approach to the treatment of chronic CHF is being reexamined. This review evaluates the role of digoxin therapy in patients with chronic CHF in light of results of relatively recent randomized trials.

DIGOXIN VERSUS PLACEBO IN TREATMENT OF HEART FAILURE PATIENTS IN SINUS RHYTHM

In 1977 Dobbs et al[18] evaluated the role of maintenance digoxin therapy in 46 stable outpatients with a history of right- or left-sided heart failure due to a variety of causes. All had been receiving prior digoxin therapy. Patients were randomly allocated to receive either digoxin (titrated to achieve a serum digoxin concentration of 1.0 ng/mL) or placebo, and after 6 weeks they were crossed over to the other treatment. Of the patients, 28 were receiving diuretics and 13 were in atrial fibrillation; however, 6 had a slow ventricular response when not taking digoxin. Sixteen of the 46 patients deteriorated while receiving placebo. Of these, 8 improved when digoxin was reintroduced. In the remainder, increasing the dose of diuretics resulted in clinical compensation. It is not clear how many of the patients who deteriorated were in atrial fibrillation. During placebo treatment, the results of pulmonary function tests deteriorated even in patients who did not show clinical evidence of worsening CHF.

TABLE I Effects of Digoxin Withdrawal on Echocardiographic Parameters at 3 Months

	Pts (n)	Digoxin	Placebo	p Value
Left ventricular end-diastolic dimension (mm)	21	55.8 ± 2.3	57.6 ± 2.2	<0.001
Velocity of circumferential shortening (circ/s)	19	0.90 ± 0.08	0.82 ± 0.06	<0.05
Fractional shortening of minor hemiaxis of left ventricle	19	0.25 ± 0.02	0.23 ± 0.02	NS

circ = circumference; NS = difference not significant.
Adapted from *Am J Med.*[19]

Fleg et al[19] studied the effects of digoxin in a double-blind crossover design trial of 30 patients in normal sinus rhythm with mild CHF, reflected by the fact that only 1 patient had a third heart sound. Of the 30 patients, 5 were receiving nitrate preparations and 23 were receiving diuretics. No patient deteriorated clinically during the 3 months of placebo administration. However, during the placebo phase, there was a significant increase in the resting left ventricular (LV) end-diastolic dimension, and a decrease in the velocity of circumferential fiber shortening on echocardiography (Table I). Maximal exercise capacity was similar during placebo and digoxin periods. This study agrees with others that observed no clinical deterioration in patients with mild CHF when digoxin was discontinued, particularly when diuretic therapy was maintained.[20] However, given the low rate of overt decompensation over short periods of time in patients with minimal CHF, it is difficult from relatively small studies like this to assess whether or not digoxin is beneficial.

Lee et al[21] conducted a crossover trial of digoxin (titrated to a serum concentration of >1.2 ng/mL) versus placebo in 25 stable outpatients in sinus rhythm who had a documented history of CHF of various etiologies. Six of 25 patients had a left ventricular (LV) ejection fraction >50%; 22 (88%) were taking diuretics, and 8 (32%) received vasodilators. The severity of CHF, according to a clinical and radiographic scoring system, was reduced by digoxin in 14 (74%) of the remaining 19 patients with systolic dysfunction. In 5 of the 14 patients who deteriorated, clinical improvement was confirmed by repeated trials (Figure 1). The overall LV ejection fraction was similar during the digoxin and placebo study periods. Patients who responded to digoxin exhibited more severe CHF (LV dilation, lower ejection fraction, and a third heart

TABLE II Comparison of Clinical Measurements During Digoxin and Placebo Phases in 19 Patients with Heart Failure

	Digoxin	Placebo	p Value
Heart rate (beats/min)	77 ± 2	83 ± 2	<0.001
Weight (kg)	65.6 ± 2.7	65.4 ± 2.9	NS
Left ventricular ejection time (msec)	388 ± 7	403 ± 6	<0.001
Preejection period (msec)	128 ± 5	138 ± 5	<0.001
Congestive heart failure score*	12 ± 0.3	13 ± 0.4	NS
Cardiothoracic ratio	0.54 ± 8	0.54 ± 8	NS

*From a minimum of 11 (absence of signs and symptoms of CHF) to the worst CHF score of 28 points.
NS = difference not significant.
Adapted with permission from *J. Cardiovasc Pharmacol.*[22]

sound). This study demonstrates that digoxin therapy is beneficial in patients with systolic dysfunction.

Taggart et al[22] studied 22 patients in New York Heart Association (NYHA) functional class I or II (1 patient was in class III) CHF with a documented history of overt CHF, using a double-blind, placebo-controlled crossover trial of digoxin. It is unclear how many patients in this study had systolic or diastolic dysfunction. All but 1 patient received diuretics. During the 3 months of observation, 14 patients showed no clinical deterioration whether they were taking digoxin or placebo; 5 patients deteriorated while taking placebo and 2 while taking digoxin; 1 patient developed digoxin intoxication. The resting heart rate was significantly lower with digoxin therapy. In addition, the LV ejection time and chest x-ray film findings, including cardiothoracic ratio, were improved during digoxin therapy compared with placebo (Table II). Although digoxin exerted a sustained positive inotropic effect during maintenance therapy, throughout this 3-month observation there were no overt clinical benefits from digoxin in most of the patients studied.

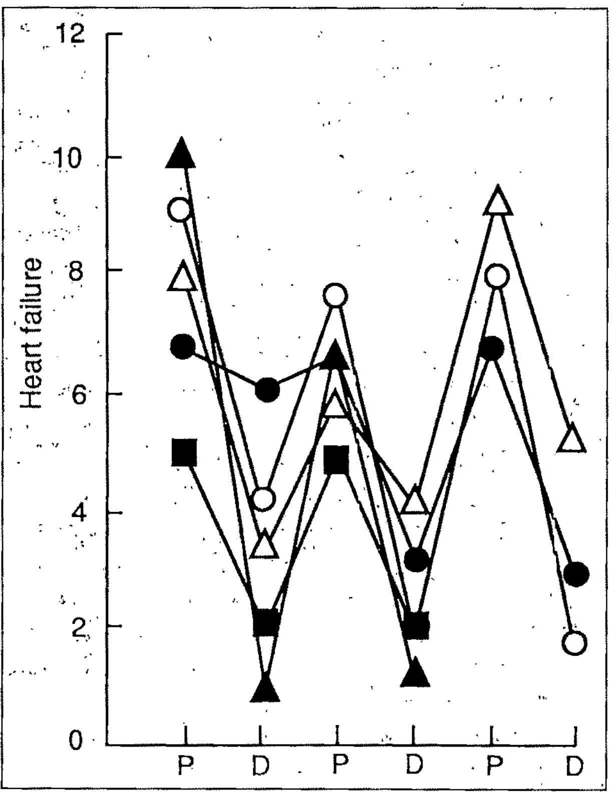

FIGURE 1. Heart failure score during placebo (P) and digoxin (D) periods. Each symbol represents one patient. (Reproduced with permission from *N Engl J Med.*[21])

TABLE III Outcome in 20 Patients with Chronic Heart Failure

	Digoxin	Placebo	p Value
Echocardiogram			
Fractional shortening (%)	21	17	0.004
Left ventricular end-diastolic dimension (cm/m²)	5.9	6.2	0.30
Six-minute walk test (m)	411	392	0.055
Congestive heart failure score*	2.3	4.4	0.001
Cardiothoracic ratio	0.53	0.58	0.04

*The maximum possible score corresponding to the worst CHF is 13 points.
Adapted from *Am J Cardiol.*[23]

Guyatt et al[23] studied 20 patients with moderately severe CHF (of these, 17 patients had ischemic dilated cardiomyopathy), using a crossover trial design. Before the study, 18 patients were receiving diuretics, 17 digoxin, and 11 vasodilators. Oral digoxin was titrated to produce a serum concentration of 1.5–2.5 ng/mL. Seven patients required premature discontinuation from the study due to worsening CHF; all 7 were receiving placebo. Echocardiographic assessment of LV function revealed improvement during digoxin treatment. In addition, the 6-minute walking distance was longer and heart size smaller with digoxin when compared with placebo (Table III). In this study, an enlarged heart, NYHA functional class III or IV CHF, and jugular venous distention (>6 cm), but not the presence of a third heart sound, predicted the response to digoxin. Although 350 patients were identified as eligible to participate in this study, only 20 were studied. The most common reason for exclusion was the refusal of the physician who thought that the patient was too sick as a result of CHF to participate in this study.

The 6-month effects of digoxin in 300 patients with mild-to-moderate CHF (ejection fraction ≥40%) compared with placebo and captopril were evaluated in a multicenter trial.[24] During the study, 84% of patients were maintained on diuretics. The LV ejection fraction increased by 4.4 and 0.9% in the digoxin and placebo-treated patients, respectively (Figure 2). Withdrawal from the study because of worsening CHF occurred in 15% of the

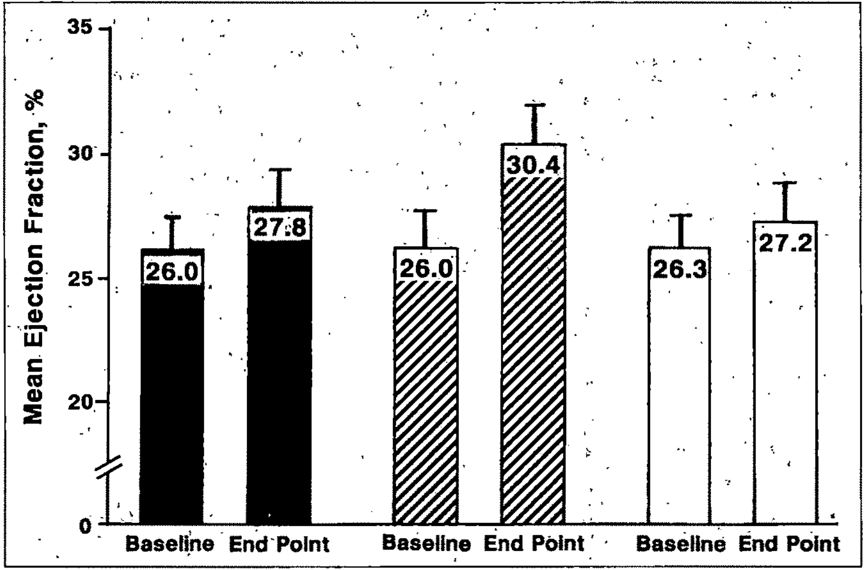

FIGURE 2. Mean (± standard error of the mean) ejection fraction at baseline and end point. Digoxin group (*slashed bars*) had significantly greater change compared with placebo (*open bars*) (p<0.01) and captopril (*solid bars*) (p <0.05) groups. (Reproduced with permission from *JAMA*.[24])

placebo-treated group compared with 4.2% in the digoxin-treated group. More patients required hospitalization or assessment in the emergency department because of worsening CHF in the placebo group (29%) compared with the digoxin treatment group (15%) (Table IV). However, when improvement in exercise time was evaluated, no significant differences were noted between digoxin and placebo groups (Figure 3). Seven patients who received digoxin died compared with 6 who received placebo. This study suggests that the combination of digoxin–diuretic is effective in maintaining patients with moderate CHF in a compensated state. The study was somewhat biased against digoxin; 164 patients were initially evaluated and 65% were receiving digoxin before entry. However, only patients whose CHF did not worsen when digoxin was discontinued during the prerandomization phase were entered into the study.

The German and Austrian Xamoterol Study Group[25] randomized 433 patients with history of CHF to digoxin, xamoterol (a partial β_1-adrenoreceptor agonist), or placebo in a 3-month evaluation study. Approximately 50% of the patients enrolled in this trial had angina pectoris, and approximately 90% were in NYHA functional class I or II CHF. LV function was not evaluated. The only criterion used for diagnosing CHF was a history of dyspnea or fatigue on exercise. Of enrolled patients, 50% were receiving digoxin before randomization, approximately 25% were receiving a diuretic, 10%, long-acting nitrates, and 5%, vasodilators. There was a trend toward increasing exercise time at 3 months of follow-up in the digoxin group (17%)

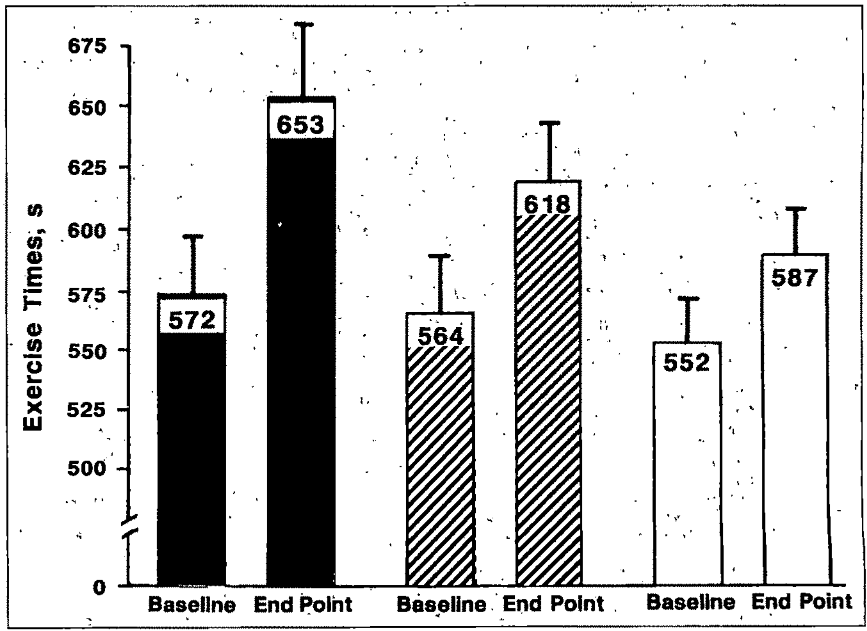

FIGURE 3. Mean (± standard error of the mean) exercise time in seconds at baseline and end point. Captopril group (*solid bars*) had significantly greater change from baseline compared with placebo group (*open bars*) (p <0.5). *Slashed bars* indicate digoxin group. (Reproduced with permission from *JAMA*.[24])

TABLE IV Hospitalization and Emergency Department Visits

Treatment Group	No. Patients Hospitalization Only	Emergency Department Visit Only	Both	Total
Captopril (n = 104)	5	7	5	17
Digoxin (n = 96)	3	7	5	15
Placebo (n = 100)	11	10	8	29*
Total	19	24	18	61

*p <0.05 vs captopril and digoxin groups.
Reproduced with permission from *JAMA*.[24]

compared with placebo (5%). Reduction of NYHA functional class by at least 1 class occurred in 24% of digoxin- and 6% of placebo-treated patients. Signs of CHF (i.e., rales and peripheral edema) occurred less often in the digoxin-treated group. There was also a significant decrease in body weight in the digoxin-treated group. The cardiothoracic ratio was reduced by 23% compared with 9% in the digoxin and placebo recipients, respectively (Figure 4). Six patients were withdrawn because of worsening CHF in the placebo group and 4 in the digoxin group. This study is particularly interesting, since it demonstrates a somewhat beneficial effect of digoxin even in patients with active (many had angina) ischemic heart disease who are in NYHA functional class I or II CHF.

Pugh et al[26] conducted a randomized crossover study of digoxin withdrawal and reintroduction over two 8-week periods in 44 patients with stable CHF and sinus rhythm; 75% received diuretics and 10% received vasodilators. None had a third heart sound. After digoxin withdrawal, clinical deterioration (heart failure or atrial fibrillation or both) occurred in 5 patients (11%) treated with digoxin compared with 16 placebo-treated patients (25%). Of the 16 placebo-treated patients, 5 did not respond to increasing diuretic doses; however, all 5 improved when digoxin was reintroduced. Using systolic time intervals, a significant increase in the ejection period was observed during placebo treatment, regardless of whether patients deteriorated clinically. This suggests that a decrease in contractility was observed even in patients who did not deteriorate clinically when digoxin was discontinued. The occurrence of clinical deterioration could not be predicted by clinical, hemodynamic, or pharmacologic measurements made before digoxin withdrawal. The deterioration when digoxin was discontinued was associated, however, with an increase in erythrocyte digoxin binding sites, rubidium-86 influx, and a decrease in intra-erythrocytic sodium concentration (Figure 5). In contrast, in patients who did not deteriorate, no changes were

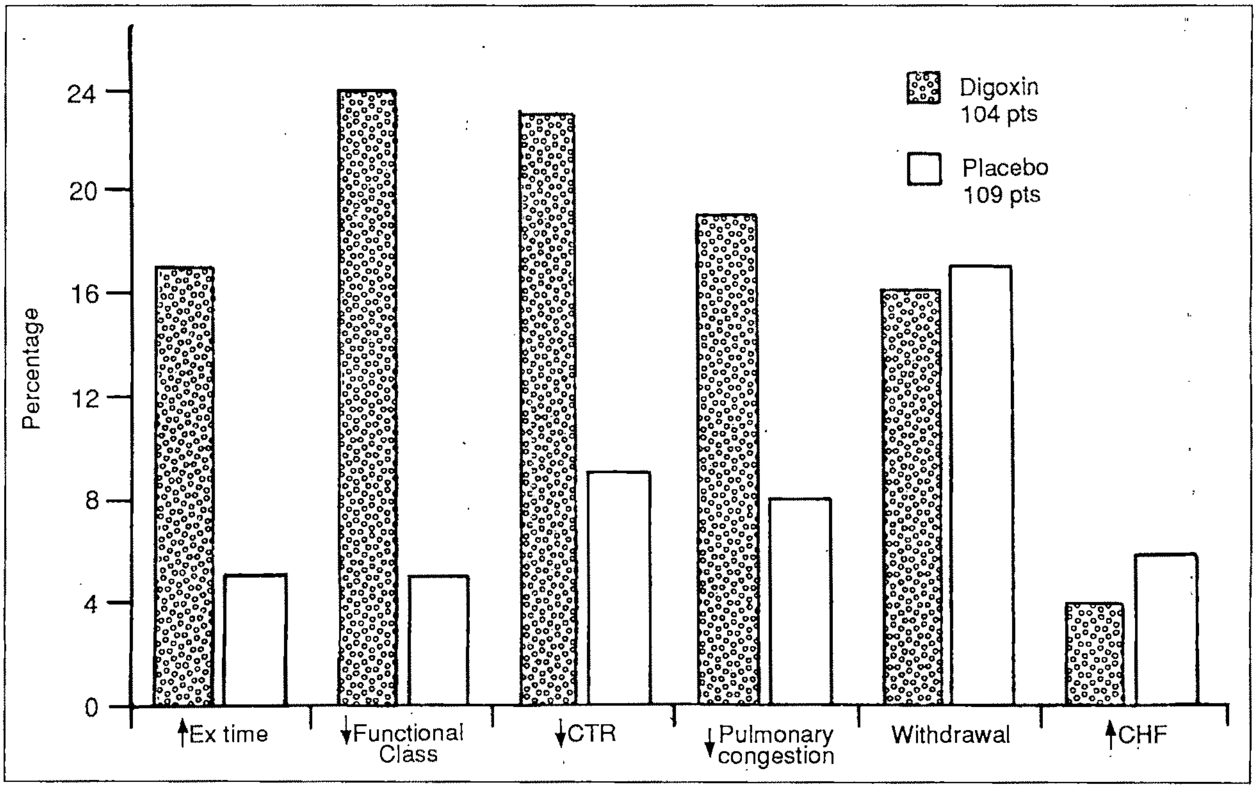

FIGURE 4. Percent increase (↑) in exercise duration and worsening of congestive heart failure (CHF) and decrease (↓) in New York Heart Association functional class, cardiothoracic ratio (CTR) and pulmonary congestion during digoxin and placebo therapy. (Adapted from *Lancet*.[25])

noted in the erythrocyte digoxin binding sites, rubidium-86 influx, or intra-erythrocytic sodium when digoxin was discontinued. However, this group of nondeteriorators had an increase in rubidium-86 influx and intra-erythrocytic sodium concentration when digoxin was reintroduced several weeks later (Figure 5). This study suggests that in some patients, tolerance to digoxin may develop over time, although tolerance may be abolished after a drug-free period.

DiBianco et al,[27] in a 12-week double-blind trial, studied the effects of digoxin, combination digoxin–milrinone, milrinone alone, or placebo in 230 patients with moderate CHF (ejection fraction approximately 25%) who were taking diuretics; 50% were also taking vasodilators. When compared with placebo, worsening of CHF occurred in only 15% of the digoxin-treated group, compared with 47% in the placebo-treated group (Figure 6). Of patients randomized to receive digoxin, 77% completed the study compared with only 47% of patients randomized to receive placebo. Both ejection fraction and exercise time increased significantly only in the patients who received digoxin. When arrhythmia occurrence was evaluated, there were no significant differences between the digoxin and placebo groups. Overall mortality was approximately 6% in both groups.

Fleg et al[28] examined the effect of maintenance digoxin therapy in a crossover design study on aerobic performance and exercise LV function when compared to placebo in 10 patients with mild-to-moderate CHF (ejection fraction <35%) due to coronary artery disease. Only 2 patients had a third heart sound. All patients were receiving diuretics and 5 were receiving vasodilators. Although none of the 10 patients noticed a significant difference in CHF symptoms or required adjustment of diuretic or vasodilator doses, there was a significant increase in ejection fraction at peak exercise despite a higher achieved afterload in the patients receiving digoxin when compared with placebo (Figure 7). Although digoxin did not enhance aerobic capacity in these ambulatory patients, it may be speculated that in the presence of an afterload-reducing agent, this increase in ejection fraction in response to digoxin may have been translated into an increase in exercise tolerance, since a significant increase in systolic blood pressure was observed in response to digoxin when compared with placebo.

The recently presented results of the Prospective Randomized Study of Ventricular Failure and the Efficacy of Digoxin (PROVED) study[29] as-

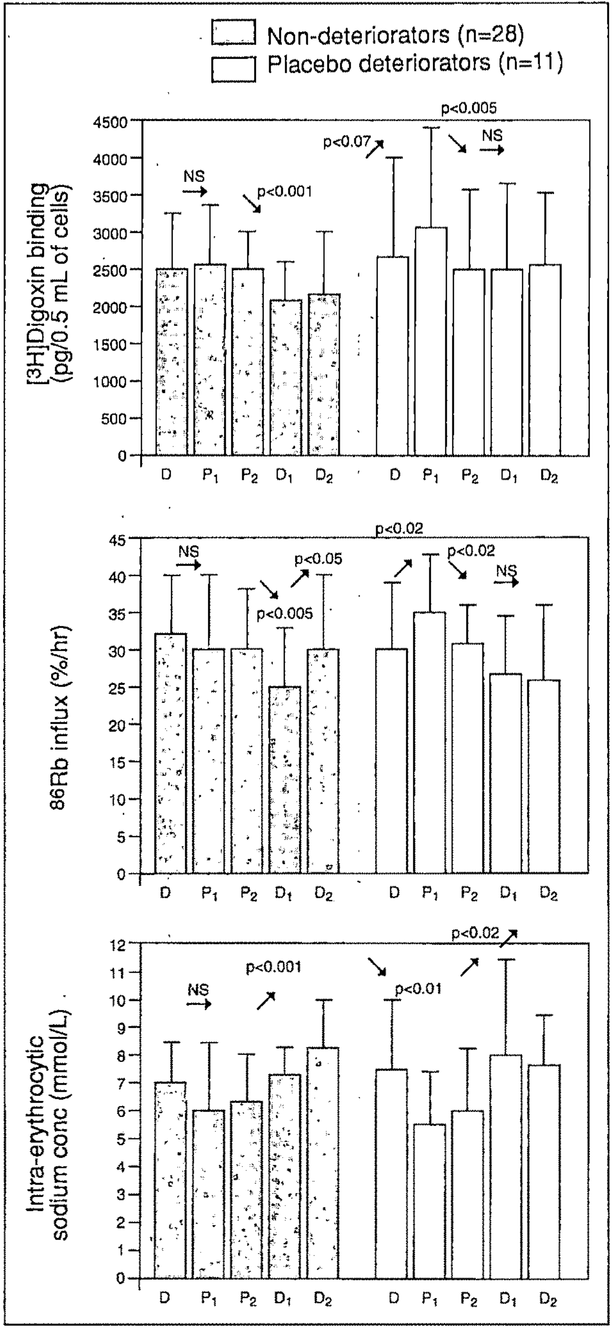

FIGURE 5. Erythrocytic [^{3}H]digoxin binding, rubidium-86 uptake, and intra-erythrocytic sodium concentrations at different study times. In the patients who did not deteriorate during the digoxin withdrawal, there was no change in either [^{3}H]digoxin binding, intra-erythrocyte sodium concentration, or uptake of rubidium-86 during the 8 weeks after withdrawal (P_2). One week after the reintroduction of digoxin (D_1), both [^{3}H]digoxin binding and uptake of rubidium-86 decreased and then increased again after 8 weeks of digoxin therapy (D_2). During digoxin reintroduction (D_1 and D_2), there was a gradual increase in intra-erythrocytic sodium concentration. In patients who did deteriorate after 1 week (P_1) of digoxin withdrawal, there was an increase in both binding sites and the rate of rubidium-86 transport. After reintroduction of digoxin, there were no changes in either binding or uptake. However, there was no increase in intra-erythrocytic sodium concentration. (Reproduced with permission from *Br Heart J*.[26])

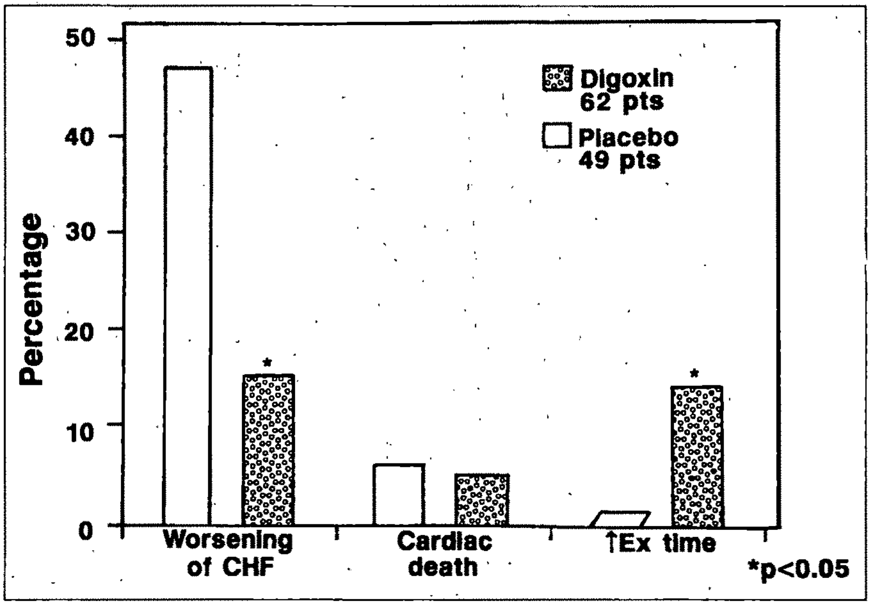

FIGURE 6. Worsening of congestive heart failure (CHF), mortality and increased (↑) exercise (Ex) duration in placebo and digoxin groups. (Adapted from *N Engl J Med*.[27])

sessed the effects of digoxin withdrawal in 88 patients with stable heart failure, and ejection fraction ≤35%, not treated with ACE inhibitors. Digoxin withdrawal was associated with hemodynamic and clinical deterioration.

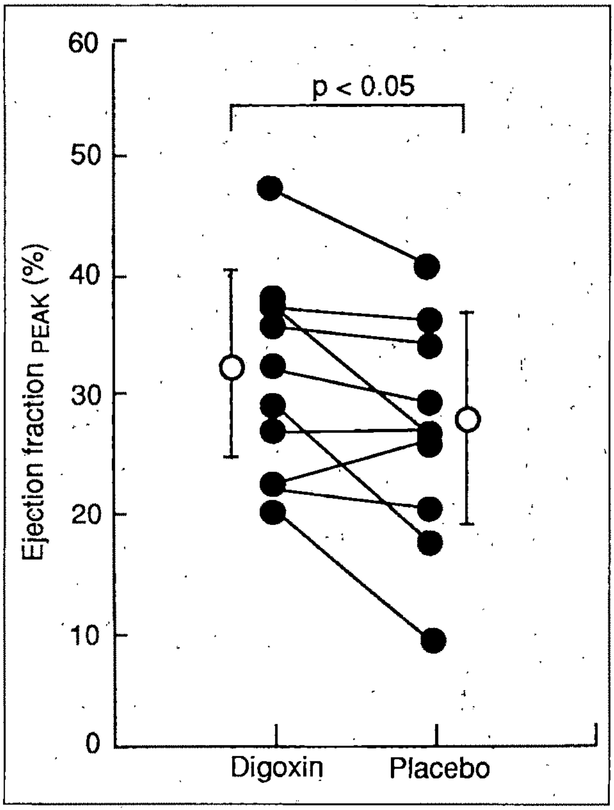

FIGURE 7. Effect of digoxin and placebo on radionuclide left ventricular ejection fraction at maximal cycle exercise in 10 patients. The higher ejection fraction noted during digoxin therapy was present despite a significantly higher systolic blood pressure at maximal exercise (177 ± 25 mm Hg) compared with placebo (165 ± 21 mm Hg). (Reproduced with permission from *J Am Coll Cardiol*.[28])

From these randomized placebo controlled trials, it can be concluded that digoxin chronically improves LV function and is effective in preventing clinical deterioration in patients with mild-to-moderate CHF due to systolic dysfunction who are in sinus rhythm (Table V). This is particularly supported by the studies that enrolled >100 patients and in which diagnosis of CHF was well documented.[24,27]

Although the severity of CHF (presence of a third heart sound, increased jugular venous distention, etc.) has been associated with clinical response to digoxin by some,[21,23] others have been unable to identify clinical characteristics of responders.[26] In fact, it is unclear if clinical criteria alone should be used to assess the so-called responders to digoxin, particularly when response can be manifested only by symptoms and signs, exercise tolerance, hemodynamics, or neurohormonal means.[30] Response assessment can be somewhat difficult, since there may be a poor correlation between clinical signs and symptoms of CHF and exercise tolerance, LV function, hemodynamics or its progression.[31–34]

DIGOXIN VERSUS ACE INHIBITORS IN TREATMENT OF HEART FAILURE

In recent years, the beneficial effects of adding ACE inhibitors to diuretics and digoxin have been clearly demonstrated in patients with chronic CHF, as judged by significant improvements in symptoms[35] and exercise tolerance[36] and a decrease in ventricular ectopy[37] and mortality.[38–40] Tolerance is not generally observed during long-term therapy with ACE inhibitors[41] and these drugs attenuate

TABLE V Double-Blind, Randomized, Placebo-Controlled Studies of Digoxin in Heart Failure Patients

Reference	Study Design	Duration (weeks)	No. Pts.	FC (NYHA)	EF (%)	Digoxin Concentration (ng/ml)	Concomitant therapy (%)		↑ ExT	Worsening of HF (%)		Decreased Risk of HF (%)	Cardiac Mortality (%)	
							D	V		Dig	P		Dig	P
Dobbs et al,[18] 1977	Crossover	6	46*	?	?	1.3	60	0	?	0	34†	100	0	0
Fleg et al,[19] 1982	Crossover	12	30	II-III	23 (FS)	1.4	76	16	No	0	0	0	0	0
Lee et al,[21] 1982	Crossover	9	25	II-III	29	1.2	88	24	?	24	56†	57	0	0
Taggart et al,[22] 1983	Crossover	12	22	I-II	?	0.8	95	31	?	10	21	52	0	0
Guyatt et al,[23] 1988	Crossover	7	20	II-III	19 (FS)	1.75	90	55	Yes‡	0	35†	100	0	0
Captopril-Digoxin,[24] 1988	Parallel	24	196§	II-III	25	0.7	84	0	No	15	29†	48	7	6
German and Austrian Xamoterol,[25] 1988	Parallel	12	213‖	I-III	?	0.9	25	10	No	4	5	20	0	0
Pugh et al,[26] 1989	Crossover	8	44	?	27 (FS)	0.8	75	9	?	11	25†	72	0	0
DiBianco et al,[27] 1989	Parallel	12	111¶	II-III	25	1.4	100	48	Yes	15	47†	68	5	6
Fleg et al,[28] 1991	Crossover	4	12	II-III	33	1.0	100	41	No	0	8	100	0	0
Total			719				•			10	30	66		

*Thirteen pts in atrial fibrillation.
†p <0.05.
‡Trend.
§Total of 300 patients, 104 were on captopril.
‖Total of 433 patients, 220 were on xamoteral.
¶Total 230 patients (59 on milrinone, 60 on milrinone + digoxin). D = diuretics; Dig = Digoxin; EF = ejection fraction; ExT = significant increase in exercise time; FC = functional class; FS = fractional shortening on echocardiogram; HF = heart failure; NYHA = New York Heart Association; P = placebo; V = vasodilator.

the central baroreceptor[42] abnormalities noted in CHF. This effect is particularly important since progression of CHF may be related to autoregulatory mechanisms, including baroreceptor function.[43]

In the Captopril–Digoxin study,[24] both digoxin and captopril were comparable in maintaining patients with mild-to-moderate CHF in a compensated state as assessed by hospitalization or emergency department visits for CHF worsening. An improvement in NYHA functional class was seen in 41% of patients receiving captopril and 31% of those receiving digoxin. The LV ejection fraction increased significantly (+4.4%) only in digoxin-treated patients, compared with a 1.8% improvement in captopril-treated patients (Figure 2). However, the exercise time increased significantly when compared with placebo only in the captopril-treated group (Figure 3). The rate of discontinuation due to adverse drug reactions was low: 2.9% and 4.2% in the captopril- and digoxin-treated groups, respectively. The greater number of possible adverse drug effects was attributed to captopril treatment (44.2% of patients vs 30.2% in the digoxin group). Captopril-associated adverse effects comprised complaints of lightheadedness in approximately one third of all drug reactions. The symptoms were relieved, however, by decreasing the diuretic dose. The mean change in blood pressure from baseline was a 6.7 mm Hg decrease in the captopril group compared with a 2.7 mm Hg increase in patients who received digoxin. Serum potassium levels increased in the captopril-treated patients and decreased in the digoxin group. Because digoxin appeared to improve LV function and increase blood pressure, and captopril decreased blood pressure and improved exercise tolerance, it is possible that long-term combination therapy with digoxin and captopril would have been superior to either drug alone, since the mechanism of action and clinical effects were different, yet complementary.

Alicandri et al[44] compared captopril with digoxin in a single-blind crossover comparison study in 16 patients taking diuretics for mild-to-moderate CHF (NYHA classes II and III) due to ischemic heart disease. This was the first study to examine the long-term effects of digoxin on plasma norepinephrine concentrations. Both digoxin and captopril reduced the plasma norepinephrine level in both supine and upright positions (Figure 8) when compared with placebo. Exercise duration was

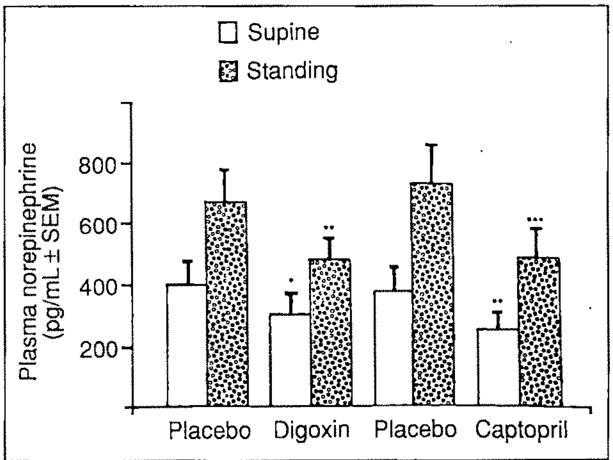

FIGURE 8. Serum norepinephrine levels (in 16 patients) in supine and standing positions during placebo, digoxin and captopril treatment. * $p < 0.05$; ** $p < 0.001$; *** $p < 0.001$ **compared with placebo. (Reproduced with permission from *J Cardiovasc Pharmacol*.[44])**

TABLE VI Echocardiographic Measurements in Enalapril and Digoxin Groups

	Enalapril		Digoxin	
	Baseline	Week 14	Baseline	Week 14
Left ventricular internal diameter at end-diastole (mm)	66 ± 7	66 ± 8	67 ± 8	66 ± 10
Left ventricular internal diamater at end-systole (mm)	55 ± 9	53 ± 10*	57 ± 10	54 ± 12†
% fractional shortening	15 ± 10	20 ± 10†	15 ± 5	20 ± 7*

*$p < 0.01$.
†$p < 0.05$.
Adapted with permission from *J Am Coll Cardiol.*[47]

increased by both drugs. The peak heart rate during exercise was higher in captopril- than digoxin-treated patients. Digoxin caused a significant increase in systolic and diastolic blood pressures. In contrast, captopril caused a significant reduction in systolic and diastolic blood pressures. This study suggests that both medications comparably maintain patients in a compensated state and that each is a valid alternative, depending on the differential effects desired (i.e., increase vs decrease in blood pressure).

Beaune et al[45] compared enalapril with digoxin in a (non–placebo-controlled) multicenter parallel randomized trial in 142 patients with a documented history of CHF. After 8 weeks of treatment, they found a significant improvement in NYHA functional class in both the enalapril- and the digoxin-treated patients. Blood pressure was decreased with enalapril but not with digoxin. Adverse events were observed in 13 patients who received enalapril versus 7 patients who received digoxin. In each group, 2 patients exhibited CHF worsening (Figure 9). No significant differences were noted in serum creatinine values; however, potassium levels increased in the enalapril recipients and decreased in the digoxin group.

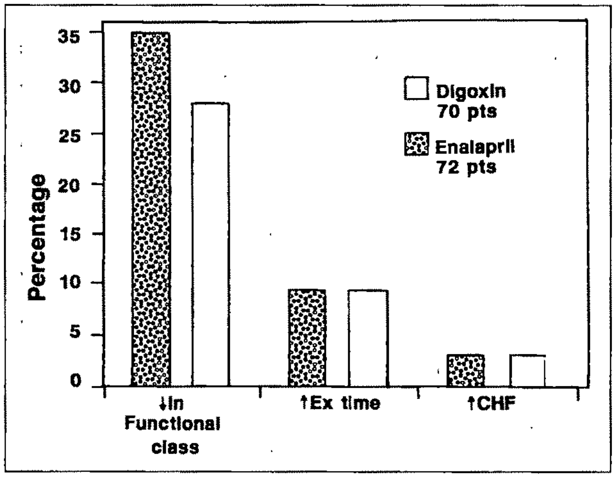

FIGURE 9. Percent decrease (↓) in New York Heart Association functional class and increase (↑) in exercise (Ex) time and worsening of congestive heart failure (CHF) during digoxin and enalapril treatment. (Adapted from *Am J Cardiol.*[45])

Kromer et al[46] examined the effects of digoxin and quinapril (an ACE inhibitor) alone and in combination in 19 patients with NYHA functional class II CHF, using a single-blind, crossover design. Quinapril, but not digoxin, increased the exercise time significantly when compared with placebo. It was interesting that the echocardiographic LV fractional shortening was increased significantly only when digoxin and quinapril were administered concomitantly (Figure 10). Quinapril, but not digoxin, decreased LV end-diastolic and end-systolic diameters. In this study, plasma norepinephrine concentrations did not change significantly in response to digoxin but were diminished in response to quinapril. Blood pressure decreased with quinapril and increased with digoxin administration.

Davies et al[47] compared the effects of enalapril and digoxin in a multicenter parallel (non–placebo-controlled) trial of 145 patients in NYHA classes II and III CHF. At 14 weeks, 13 patients receiving enalapril showed improvement (reduction of at least 1 NYHA functional class) and 9 deteriorated (increase of at least 1 NYHA functional class) compared with 14 patients who improved and 22 patients who deteriorated in the digoxin group

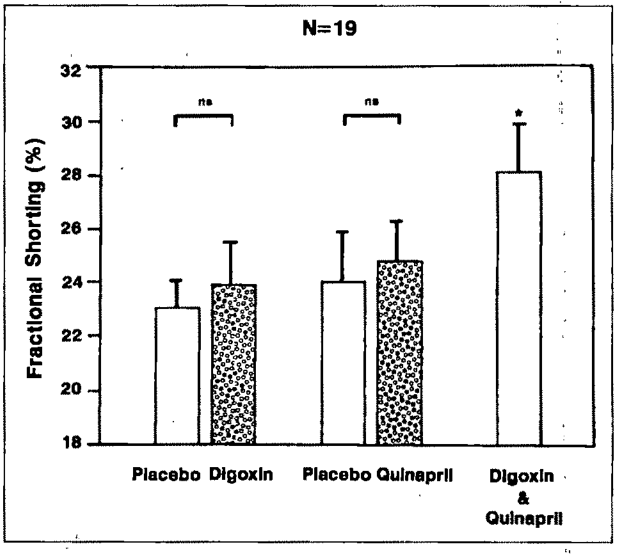

FIGURE 10. Left ventricular echocardiographic fractional shortening in 19 patients with New York Heart Association functional class II congestive heart failure and sinus rhythm before and 6 weeks after treatment with digoxin, quinapril or the combination of both drugs. *$p < 0.03$ versus digoxin and versus quinapril. (Reproduced with permission from *J Cardiovasc Pharmacol.*[46])

TABLE VII Clinical Outcome at Week 14 in 145 Patients Taking Enalapril or Digoxin

	Enalapril		Digoxin	
	No.	%	No.	%
Improvement	13	18	14	19
No change	50	69	37	51
Worsening	9	13	22	30*
Total	72		73	

*$P < 0.025$. If the only patients who withdraw for definite symptoms of CHF are analyzed, the difference between groups is not statistically significant.

Improvement is defined as lowering of New York Heart Association functional class, worsening as an increase in functional class or discontinuation because of an adverse clinical event.

Adapted with permission from *J Am Coll Cardiol.*[47]

(Tables VI and VII). Two patients (2%) were withdrawn in the enalapril group and 7 patients (10%) in the digoxin group because of exacerbation of CHF. Exercise time and LV ejection fraction improved in both groups. Enalapril caused a decrease in both diastolic and systolic blood pressure. An increase in systolic blood pressure and a decrease in heart rate were associated with digoxin. Similar changes in blood pressure and heart rate were observed during exercise in both groups. No patient died during the study.

From these studies, it appears that both digoxin and ACE inhibitors are useful in the management of CHF (Table VIII). Digoxin may increase blood pressure and decrease heart rate and serum potassium concentrations. ACE inhibitors tend to decrease blood pressure and increase heart rate and serum potassium concentrations. Both agents may increase exercise tolerance and ejection fraction and decrease plasma norepinephrine concentrations. It should be recognized, however, that only ACE inhibitors have been shown to increase survival in patients with CHF.[38–40] Since in those trials[38–40] that assess survival most of the patients were receiving digoxin and diuretics, it is not known if ACE inhibitors alone would have had a similar beneficial effect, particularly since stabilization of patients with CHF is difficult to achieve when ACE inhibitors are used alone.[48]

DIGOXIN VERSUS NEWER AGENTS IN TREATMENT OF HEART FAILURE

The German and Austrian Xamoterol multicenter trial[25] studied the 3-month effect of digoxin, xamoterol, and placebo in 400 patients with mild CHF in a double-blind randomized parallel study. As stated previously, a history of heart failure was not documented, LV function was not assessed, and >50% continued to have angina during the study. Of the 213 xamoterol-treated patients, 5 demonstrated worsening of CHF versus 4 of the 101 digoxin-treated patients. This study suggests that in patients with minimal CHF and angina, xamoterol is somewhat superior to digoxin in increasing exercise duration. Since many of the patients who entered this study had angina, this finding is not surprising, because xamoterol may have an antianginal effect due to its β_1-adrenoreceptor antagonistic effects.[49] However, in another study of 516 patients with NYHA functional class III–IV CHF who were randomized to xamoterol or placebo, the mortality at 13 weeks of follow-up was higher in the xamoterol group (9.1%) compared with the placebo group (3.7%).[50]

DiBianco et al[27] compared milrinone with digoxin alone and with the combination of milrinone and digoxin versus placebo. Worsening of

TABLE VIII Randomized, Double-Blind Trials in Patients with Heart Failure in Sinus Rhythm Comparing Digoxin with ACE Inhibitors

Reference	Study Design	No. Pts.	FC (NYHA)	Duration (weeks)	↑ EF Percentage Points Compared with Baseline		↑ ExT (%) Compared with Baseline		Worsening CHF (%)		Cardiac Mortality (%)		Attenuation of Neurohormonal Abnormalities	
					Dig	ACEI	Dig	ACEI	Dig	ACEI	Dig	ACEI	Dig	ACEI
Alicandri et al,[44] 1987	Crossover (captopril)	16	II-III	4	?	?	27	35	0	0	0	0	Yes	Yes
Captopril-Digoxin,[24] 1988	Parallel (captopril)	300†	II-III	24	4.4‡	1.8	10	14	16	16	7	8	?	?
Beaune,[45] 1989	Parallel (enalapril)	142	I-IV	8	?	?	9	8	3	3	0	0	?	?
Kromer et al,[46] 1990	Single-blind crossover (quinapril)	19	II	6	1(FS)	1(FS)	4	6	0	0	0	0	No	Yes
Davies et al[47] (1991)	Parallel (enalapril)	145	II-III	14	5(FS)	5(FS)	12	8	30	13	0	0	?	?

*Versus placebo, $p < 0.05$.

†One hundred patients randomized to placebo.

‡< 0.05.

ACEI = angiotensin-converting enzyme inhibitor; CHF = congestive heart failure; FS = fractional shortening on echocardiography; other abbreviations as in Table V.

TABLE IX Randomized Double-Blind Trials in Heart Failure Patients Comparing Newer Agents with Digoxin

Reference	Study Design	No. Pts.	FC (NYHA)	Duration (weeks)	↑ EF Compared to Baseline		↑ ExT (%) Compared to Baseline		Worsening HF (%)		Cardiac Mortality (%)	
					Dig	Xam	Dig	Xam	Dig	Xam	Dig	Xam
German and Austrian Xamoterol[25] 1988	Parallel (xamoterol)	433†	I-III†	12	?	?	18	33‡	4	2	0	0
					Dig	Mil	Dig	Mil	Dig	Mil	Dig	Mil
DiBianco et al,[27] 1989	Parallel (milrinone)	230§	II-III	12	1.7‡	0.2	14	19	15	34‡	5	12
					Dig	Ibo	Dig	Ibo	Dig	Ibo	Dig	Ibo
Alicandri et al,[51] 1989	Crossover (ibopamine)	10	II-III	2	?	?	34	32	0	0	0	0

*Only 13% in NYHA functional class III.
†109 patients randomized to placebo, 104 to digoxin and 220 to xamotero.
‡$p < 0.05$ vs placebo.
§Sixty patients received milrinone plus digoxin, 49 patients received placebo.
Ibo = ibopamine; Mil = milrinone; Xam = xamoterol; other abbreviations as in Table V.

CHF occurred in only 15% of patients receiving digoxin compared with 34% of patients receiving milrinone, and 17% of patients receiving combined therapy. Of patients randomized to receive digoxin, 77% completed the study compared with only 49% of patients randomized to receive milrinone and 60% of patients randomized to receive the combination. The exercise time increased significantly with digoxin, milrinone, and their combination. There was a trend toward increased mortality in response to milrinone (12%) compared with 5% mortality in the digoxin-treated group. The ejection fraction increased significantly only in patients who received digoxin. There was also a suggestion of an increased frequency of ventricular arrhythmias in the milrinone, but not in the digoxin, treatment groups. From this study, it appears that digoxin is superior to milrinone in treating chronic CHF.

Alicandri et al[51] examined the effects of ibopamine (a dopamine derivative) with digoxin in patients with moderate CHF (NYHA classes II and III). At the end of a 5-day washout period, 10 patients were randomly assigned to receive either ibopamine or digoxin in a double-blind fashion. After 10 days of active treatment, drug therapy was washed out and patients were crossed over to the opposite treatment group. At baseline and at the end of the 2 washout periods, patients performed a handgrip and bicycle ergometer test. Both ibopamine and digoxin improved cardiac response to both types of exercise compared with the washout phase. No difference was noted between the 2 groups in improvement of exercise tolerance.

It can be concluded that, at this time, digoxin may be superior to the newer agents in treating patients with CHF (Table IX), particularly when an increase in mortality was observed with the newer inotropic agents[50,52–54] and calcium antagonists.[55]

COMBINATION THERAPY: DIGOXIN AND ACE INHIBITORS

Because of the complex pathophysiology of CHF and its progressive nature, it is unlikely that one drug can control its signs and symptoms and improve survival.[56] This is particularly true since all classes of drugs used to treat chronic CHF have therapeutic limitations and side effects. In addition, each drug's effectiveness may be different from one period of the disease to another, based on the fluctuation of hemodynamic or neurohormonal abnormalities over time. At present, the oral treatment of chronic CHF consists of diuretics, digoxin, vasodilators, and ACE inhibitors.[56] Diuretics may activate the neuroendocrine systems,[57] deplete the body of potassium and magnesium, and may aggravate arrhythmias.[58,59] Digoxin increases cardiac contractility, improves hemodynamics, and improves exercise tolerance. Its effect on survival is not yet known.[60] Vasodilators such as hydralazine may not be able to control signs and symptoms of CHF without a diuretic,[61] and may cause significant side effects requiring discontinuation of the drug.[62] ACE inhibitors improve survival when combined with diuretics and digoxin.[38] However, they may decrease cardiac contractility[63] and do not maintain patients in a compensated state when used alone.[48] Theoretically, the undesirable effects of one class of drugs (i.e., diuretics, digoxin, or vasodilators) may be counterbalanced by the addition of a medication from another class. For example, the decrease in blood pressure observed with ACE inhibitors may be attenuated with concurrent digoxin therapy.[46] Potential peripheral vasoconstrictive effects of digitalis may be prevented by ACE inhibitors.[64]

Digoxin and ACE inhibitors achieve salutary effects in patients with CHF by different mechanisms—the former by increasing cardiac contractility[65] and possibly restoring baroreceptor responsiveness,[66,67] and the latter by vasodilation[68] (via prostaglandin stimulation and angiotensin II blockade) and possible preservation of functional myocardial tissue through effects on the coronary circulation,[69] on contractile[70] and interstitial tissues,[71] and by preventing or restoring the downregulation of β receptors.[72] It is possible that the combined use of digoxin and an ACE inhibitor is more beneficial than the use of either drug alone.[73] In addition, the combination may obviate the need for maximal doses of diuretics and thereby reduce side effects associated with this therapy (e.g., electrolyte abnormalities). We[74] have seen that the acute administration of the digoxin–captopril combination has an additive effect in improved rest and exercise hemodynamics, ejection fraction, and exercise time. However, it is not known if these apparent beneficial effects noted in patients with severe heart failure during acute administration of the combination of two drugs are sustained.

In a small, single-blind, crossover trial, Kromer et al[46] examined the efficacy of digoxin, quinapril, and their combination in 19 patients with minimal CHF (NYHA class II) and observed that LV function was improved significantly by the combination but not by either drug alone. However, little can be concluded from a study like this, which evaluated only 19 patients with very mild CHF.

The CONSENSUS Trial[38] showed that the addition of an ACE inhibitor to digoxin and diuretics prolongs life in patients in NYHA functional class IV CHF. However, it is not clear whether it was the combination of diuretics, digoxin, and ACE inhibitors or the ACE inhibitor itself that was responsible for prolonging life. The clinical value of combining digoxin with ACE inhibitors was addressed by the recently presented study entitled "Randomized Assessment of Digoxin on Inhibitors of the Angiotensin Converting Enzyme" (RADIANCE).[75] This study was a multicenter, double-blind, placebo-controlled study of digoxin withdrawal conducted in 178 patients in sinus rhythm with chronic CHF due to systolic dysfunction receiving concurrent ACE inhibitors. Digoxin withdrawal was associated with clinical and hemodynamic deterioration and a decrease in exercise capacity.

Limitations of the randomized trials: Available data from randomized trials demonstrate that digoxin therapy is of benefit in patients with CHF.[76] It is not surprising that some did not observe a significant effect from digoxin, since they used a small number of patients,[19,22,26,28] the observation period was relatively short,[19,28] and the clinical event rate (worsening of CHF and/or mortality) was low[19,24,25] in the placebo groups. In addition, in some studies,[24,25] the patients enrolled were previously receiving digoxin. A selection bias may be introduced by selecting only patients who do not decompensate when digoxin is discontinued. Diuretics were commonly used, but very few patients received vasodilators.

Since the LV function was not always assessed,[18,25] CHF may have been due to systolic or diastolic dysfunction, or both, leading to the potential of variable response secondary to etiology alone. The history of CHF often was not always well documented.

Possible beneficial end points include improvement in symptoms, decreased fluid retention, improved LV function by noninvasive assessment, invasive hemodynamic evaluation, objective evaluation of improved functional capacity (i.e., exercise performance), and improved survival.[30,77] The most consistently used and therefore relevant comparable end point was the degree to which signs and symptoms of CHF improve or worsen with treatment.[76] However, for patients with chronic CHF, response to digoxin and other agents may be evaluated most thoroughly by a combination of hemodynamic, neurohormonal, and clinical assessment criteria.[30] This is particularly important because there is a poor correlation between chest radiographic findings and the signs, symptoms, and severity of CHF.[31–34] In fact, studies that attempted[24,27] to assess responders from clinical, LV function, and exercise tolerance standpoints to delineate the full potential benefits of therapeutic agents showed a clear beneficial effect from digoxin.

Benefit assessment of digoxin therapy: In a recent meta-analysis of 7 double-blind randomized controlled trials, Jaeschke et al[78] calculated the odds ratio for clinical deterioration of CHF while patients were receiving digoxin versus placebo to be 0.28 (95% confidence intervals, 0.16–0.49). This meta-analysis demonstrates that patients in sinus rhythm with mild-to-moderate CHF derived a clinically important benefit from digoxin. Since the CHF is a chronic and progressive disease, these results should be considered in light of the short observation period, the low event rate in the control group, and the difficulty in predicting which CHF patients would or would not benefit in the short term from digoxin. In addition, there may in fact be no association between clinical nondeterioration over a relatively short period of time and a deterioration in hemodynamics, LV function, and neurohormonal status.[31-34] This is particularly relevant, since improvement in hemodynamics,[79] in LV function,[80] and in attenuation of neurohormonal abnormalities[81] may be important for improving survival.

In addition to the clinical benefits from digoxin therapy, prevention of worsening of CHF over a relatively short period may have significant economic implications. Since approximately 2.5 million persons are currently estimated to have CHF in the United States and 40% of patients with CHF are hospitalized each year,[82] preventing CHF hospitalization may translate into substantial savings (approximately $5,000 per admission), particularly since digoxin therapy is not costly, is easy to administer, and intoxication from the drug is not commonly seen.[83]

Clinical implications: Digoxin is clearly the drug of choice for the treatment of CHF in patients with atrial fibrillation. However, digoxin alone, given its predominantly vagal effects, may not always slow the conduction through the atrioventricular node despite therapeutic serum concentrations during exercise or in patients with a high sympathetic tone. In these patients the addition of small amounts of β-adrenergic blocking agents or a calcium antagonist like diltiazem or verapamil is helpful in potentiating the action of digoxin on the atrioventricular node to controlling the ventricular response.

The major goal with patients in sinus rhythm is to demonstrate that digoxin in a multidrug approach to the treatment of chronic CHF improves the quality and quantity of life. The National Heart, Lung, and Blood Institute and the Department of Veterans Affairs Cooperative Studies Program are presently conducting an international, double-blind, randomized, controlled clinical trial (Digitalis Investigation Group, DIG) of patients with CHF to assess the effect of digoxin in addition to ACE inhibitors on mortality. A total of 10,000 patients with CHF and an ejection fraction $<45\%$ will be randomized to receive either digoxin or placebo. The results are expected to be published by 1996.

Until this important study is completed, based on the results of randomized placebo-controlled trials, it appears that digoxin therapy is beneficial, alone or in combination with ACE inhibitors, in patients with any signs and symptoms of CHF due to systolic dysfunction.

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DISCUSSION

Dr. Lewis: I get the impression that the more beneficial effect of digoxin occurs primarily in patients with advanced heart failure. It appears a little harder to demonstrate this effect in patients with NYHA functional class II disease, as was done with captopril.

Dr. Gheorghiade: Studies that evaluated the effects of digoxin in patients with mild CHF enrolled relatively few patients, who were followed over a short period of time. In those studies, worsening of the heart failure occurred infrequently in the control group. One will probably have to follow patients like this for a longer period to observe a clinical benefit. However, even in those studies conducted in patients with mild CHF, there was a deterioration in left ventricular function over a short period of time that was not associated with clinical deterioration. Clearly, patients who are sicker will deteriorate more rapidly compared with patients with mild CHF. That is why digoxin may appear to be more beneficial in patients with severe heart failure.

Dr. Creager: I do not think most of us would argue with the fact that digoxin has hemodynamic and clinical efficacy in terms of exercise capacity. Various studies in heart failure have advised caution in using digoxin because of its unclear effect on prognosis. The issues raised with digoxin are more concerned with its effect on survival than with its effect on functional capacity.

Dr. Gheorghiade: To date, there is no evidence to suggest that digoxin will increase mortality or, for that matter, decrease mortality in patients with CHF or after myocardial infarction.

Dr. Yusuf: You obviously have hit the nail right on the head: survival is the major issue. If you knew the magnitude of digoxin's effect on mortality versus its benefit, you still might opt to use it in patients with severe heart failure. Then, the question becomes, what do you do if digoxin improves their condition to the extent that they ultimately present with a lesser degree of heart failure? The issue of mortality becomes more critical in patients with milder cardiac dysfunction, since fewer cases deteriorate clinically over a given period. We need to know digoxin's risk–benefit ratio over the entire clinical spectrum.

Having said that, there is no evidence that digoxin actually adversely affects mortality, although the question has been raised. That is one question we can answer in our trials.

The second issue is, who benefits? The Lee study reported it was patients with cardiomegaly, a lower ejection fraction, a third heart sound, and a variety of other things, but other studies contradict these findings. Obviously, we hope our trial at the National Heart, Lung, and Blood Institute will be able to address this.

The third and most difficult issue is, what is the correct dose? I do not think we know the most efficacious dose for any drug in heart disease. The doses of digoxin we have decided to use are based on studies in atrial fibrillation, where you can look at the reduction in ventricular rate. There may be a complete dissociation between the chronotropic response and the inotropic response. There may be a complete dissociation between the inotropic response and the peripheral and sympathetic response. And who knows what impact all these variables will have on something like proarrhythmic effect?

In our trial we have used current thinking and titrated, using an algorithm, a dose that is at the lower end of the therapeutic range. Dr. Packer has often told me that subtherapeutic doses may be all that is needed and that high doses may be harmful.

Dr. Gheorghiade: Are high doses of digoxin sympatho-excitatory?

Dr. Packer: The sympatho-excitatory effects of digoxin have not been seen in patients with heart failure.

Dr. Gheorghiade: Dr. Yusuf, based on the Studies of Left Ventricular Dysfunction (SOLVD), would you treat an asymptomatic patient with systolic left ventricular dysfunction?

Dr. Yusuf: The prevention trial data are not yet final, so I cannot answer that. However, in patients with a low ejection fraction and CHF, I think giving an angiontensin-converting enzyme (ACE) inhibitor as early as possible makes sense.

Dr. Gheorghiade: Would you later add digoxin, or use the 2 agents in combination from the beginning?

Dr. Yusuf: In SOLVD, prior to entry 67% of the patients were receiving digoxin, 33% were not. The effect of ACE inhibitors was identical in these 2 groups. However, this study does not address the effects of adding digoxin to ACE inhibitor therapy. I am currently involved in a study comparing digoxin and placebo in patients already receiving an ACE inhibitor. Dr. Packer is also performing a similar trial in a smaller number of patients.

Dr. Gheorghiade: Intravenous digoxin for CHF or atrial fibrillation has been challenged by Dr. Ewy in an editorial in *Journal of the American College of Cardiology* in 1990. What is your opinion about this?

Dr. Leier: Compared with many other agents, intravenous digoxin appears to have a beneficial hemodynamic effect. On the other hand, it has a long half-life, so if you get an undesirable effect, you are stuck with it for a while. In contrast with other agents, intravenous digoxin may, in fact, reduce sympathetic tone and reduce renin and aldosterone levels, reductions that we would generally like to see.

Need for a Large Randomized Trial to Evaluate the Effects of Digitalis on Morbidity and Mortality in Congestive Heart Failure

Salim Yusuf, MBBS, FRCP, DPhil, Rekha Garg, MD, MS, Peter Held, MD, and Richard Gorlin, MD

Despite major advances in the prevention and treatment of cardiovascular diseases, the incidence and prevalence of congestive heart failure (CHF) have been increasing in recent years. As the average age of the population increases, the prevalence of CHF is expected to continue to increase. The number of deaths in which CHF was considered the underlying or contributing cause increased from 51,000 in 1955 to 274,000 by 1988 in the United States. Even accounting for population growth and an increase in the number of elderly, this represents a 2-fold increase. Additionally, CHF was responsible for about 643,000 hospitalizations in 1988. Digitalis is one of the drugs most commonly prescribed for CHF and has been used for >200 years. In 1990, digoxin was one of the most commonly prescribed drugs in the United States, accounting for >21 million prescriptions. There has been little decline in the drug's use over the last 5 years, indicating that newer treatments for CHF have not replaced the widespread use of digitalis. Despite these findings, considerable controversy surrounds the appropriateness of its role and value in treating CHF patients who are in sinus rhythm. A number of recent, uncontrolled studies have arrived at apparently contradictory conclusions concerning the effects of digitalis on mortality in postmyocardial infarction and heart failure patients. A large, double-blind, randomized, controlled clinical trial to evaluate the effects of digitalis on mortality, morbidity and quality of life is being sponsored by the National Heart, Lung, and Blood Institute in conjunction with the Department of Veterans Affairs Cooperative Studies Program. Patients with CHF and an ejection fraction ≤0.45 will be randomized to receive digoxin or placebo along with other standard therapy. Patients with an ejection fraction >0.45 also will be enrolled in a parallel but separate ancillary study. Patient recruitment started in early March 1991, and about 7,500 to 8,000 patients are expected to be enrolled over 3 years and followed for a minimum of 2 further years or until the end of the study. Results are expected to become available in 1995 or 1996.

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Despite major advances in the prevention and treatment of cardiovascular diseases, as is evident from a substantial decline in mortality due to acute myocardial infarction and strokes in the United States, national statistics indicate that the incidence and prevalence of congestive heart failure (CHF) have been increasing in recent years. About 2.5 to 3 million individuals are currently estimated to have CHF in the United States. With the continuing increase in the proportion of elderly in the population, the prevalence of CHF is expected to continue to rise. The number of deaths in which CHF was considered to be the underlying or contributing cause increased from 51,000 in 1955 to 274,000 by 1988 in the United States.[1] Even accounting for population growth, this represents a 2-fold increase. The mortality rate among CHF patients is about 50% at 5 years following diagnosis, and the age-adjusted death rate increased 21% in the 10-year period from 1968 to 1978. Additionally, CHF was responsible for about 643,000 hospitalizations in 1988 and is currently the leading diagnostic-related group in the United States among hospitalized patients over the age of 65 years. About 30% to 40% of patients with CHF are hospitalized every year. Approximately half of these hospitalizations are for worsening CHF. These limited data indicate that CHF is

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likely to remain a major clinical and public health problem in the United States. Moreover, patients with CHF have impaired quality of life, restrictions in functional capacity and a plethora of symptoms. Therefore, treatments should be evaluated for their effects on mortality, hospitalizations, quality of life and symptoms. Of the commonly used drugs for heart failure, only angiotensin-converting enzyme (ACE) inhibitors have been formally evaluated for their effects on all the end points just mentioned. Three independent randomized trials and an overview of the results of several smaller trials have established that ACE inhibitors reduce mortality and hospitalizations, improve functional status, relieve symptoms and probably have a small favorable impact on quality of life.[2-5]

Digitalis preparations are among the drugs most commonly prescribed for CHF and has been used for >200 years. In 1990, digoxin was also one of the most prescribed drugs in the United States, accounting for >21 million prescriptions.[6] There has been little decline in the drug's use over the last 5 years, indicating that newer treatments for CHF have not replaced the widespread use of digoxin, as noted by Jolly (oral communication, January 1988). In the treatment trial of the Studies of Left Ventricular Dysfunction (SOLVD),[2] 60% of patients with CHF and an ejection fraction <0.35 received digoxin at entry into the study. In the SOLVD registry of >6,000 patients with heart failure or an ejection fraction <0.45, digoxin was used in 45% of patients.[7] Moreover, data from Worcester, Massachusetts, on the use of various drugs in patients with acute myocardial infarction indicate that about 40% of discharged patients take digoxin[8]; this proportion has remained unchanged during the last 10 years.

TRIALS OF DIGOXIN IN HEART FAILURE

Despite the widespread use of digitalis and its availability for some 2 centuries, considerable controversy surrounds its role in treating CHF patients and its effect on survival. Table I lists the 15 randomized controlled trials of digitalis in CHF that have been identified.[9-20] The first 2 trials enrolled patients without clear evidence of CHF,[9,10] and the third included patients with atrial fibrillation.[11] Several small trials evaluated patients with CHF by using a crossover design with treatment periods of 2 to 3 months each.[12-16,20] Almost all patients were withdrawn from previous chronic use of digitalis and randomized to receive placebo or digoxin.

Lee et al[12] found a significant improvement in heart failure score (based on clinical and radiographic changes) in the digoxin-treated patients, although similar numbers of patients deteriorated clinically during the control and active treatment phases. Retrospective analyses suggested that a third heart sound, an enlarged heart and a low ejection fraction correlated with benefit among responders. No improvement in ejection fraction was found with digoxin. Fleg et al[13] reported no difference in exercise capacity, physical findings or symptoms between the digoxin and placebo arms in a study of 40 patients. Taggart et al[14] found no clear evidence of a benefit with digoxin in 22 patients (worsening CHF developed in 4 patients given placebo vs 2 given digoxin). After screening 380 patients, Guyatt et al[15] included 30 patients in their study and reported results obtained in the 20 who completed treatment. Patients benefited with respect to symptoms, clinical assessment of CHF, exercise capacity (6-minute walking distance) and ejection fraction during the digoxin period compared with the placebo phase. The large proportion of patients excluded or with missing end point data makes interpretation of the results difficult.

In a double-blind crossover study, Pugh et al[16] studied 44 patients and observed that 11 (25%) deteriorated clinically while taking placebo compared with only 5 who deteriorated (11%) while receiving digoxin. Most patients who deteriorated, however, could be stabilized by increasing the dose of diuretics. Only 2 patients required reintroduction of digoxin. Benefit from digoxin could not be predicted based on a third heart sound, hemodynamic criteria, echocardiographic measures or heart size. Differences in clinical response were paralleled by variations in digoxin's ability to inhibit sodium–potassium adenosine triphosphatase pump activity in the erythrocyte (measured by decreases in rubidium fluxes). Patients who were not clinically responsive to digoxin, for example, demonstrated a lack of sustained inhibition of rubidium fluxes despite continued increases in digoxin binding. Thus, there may be an adaptive response by which sodium–potassium adenosine triphosphatase is induced in the red cell membrane, which overrides the digoxin effect in some patients. Whether these results apply to the myocytes can be only conjectural at this time.

Four larger trials[17-19] compared digoxin with placebo or a second active drug. However, only the results comparing the digoxin group to the placebo group will be discussed. In the captopril-digoxin trial,[17] 196 patients were randomized to receive digoxin or placebo. All patients had an ejection

TABLE I Randomized, Controlled Trials of Digitalis in CHF

Reference	Design	No. Pts.	Digoxin Dose, mg/day (mean)	Mean Plasma Concentration	Treatment Duration	Comments	Results
Starr, Luchi,[9] 1969	Withdrawal crossover	12	0.1*	—	4 wk	Probably not CHF patients	No effect on cardiac function
Kirsten et al,[10] 1973	Withdrawal crossover	22	0.25	—	6 mo	Not all patients with CHF	Five of 22 patients had recurrence of heart failure or arrhythmia after digoxin withdrawal
Dobbs et al,[11] 1977	Withdrawal crossover	46	0.125–0.5	1.4 ng/mL	6 wk	Thirteen patients with atrial fibrillation	Sixteen of 46 patients developed signs or symptoms of CHF after digoxin withdrawal
Lee et al,[12] 1982	Withdrawal crossover	35	0.125–1.0	> 1.2 ng/mL	2.5 mo	NYHA I-III	Fourteen of 25 patients had reduction in severity of CHF. Response to digoxin correlated with the presence of S_3 and dilated heart
Fleg et al,[13] 1982	Withdrawal crossover	40	0.125–0.5 (0.24)	1.4 ng/mL	3 mo	NYHA II-IV	Withdrawal of digoxin produced a small increase in cardiac size and decrease in velocity of circumferential fiber shortening. No effect on exercise tolerance or symptoms of CHF
Taggart et al,[14] 1983	Withdrawal crossover	22	?	1.2 ng/mL	3 mo	95% NYHA I-II	Digoxin exerted a sustained positive inotropic effect during maintenance therapy but did not appear clinically to benefit the majority of patients
Guyatt et al,[15] 1988	Withdrawal crossover	30	(0.39)	1.75 nmol/L	7 wk	NYHA I-III	Digoxin improved quality of life and exercise capacity
Captopril-Digoxin,[17] 1988	Withdrawal parallel	196	0.125–0.375	0.7–2.5 ng/mL	6 mo	85% NYHA I-II	Small nonsignificant improvements in exercise time and NYHA class but significant increase in ejection fraction with digoxin compared to placebo
Xamoterol-Digoxin,[18] 1988	Withdrawal parallel	204	0.25	0.87 ng/mL	3 mo	87% NYHA I-II	Nonsignificant increase in exercise duration in the digoxin group compared to placebo group. Also, digoxin reduced signs of CHF with a marked reduction in weight
Milrinone-Digoxin,[19] 1989	Withdrawal parallel	111	0.125–0.5	1.2 ng/mL	3 mo	NYHA II-IV	Digoxin increased exercise time and EF and reduced frequency of worsening CHF
Pugh et al,[16] 1989	Withdrawal crossover	44	?	0.8–2.0 ng/mL	8 wk	NYHA II-III	Withdrawal of digoxin resulted in clinical deterioration of 25% of patients and occurrence could not be predicted by any clinical, hemodynamic or pharmacologic measurements made prior to withdrawal
Fleg et al,[20] 1991	Withdrawal crossover	10	0.125–0.50 (0.28)	1.4 ng/mL	4 wk	80% NYHA II	Digoxin did not increase exercise capacity despite improvements in left ventricular function
Young et al,[21] 1992	Withdrawal parallel	88	0.125–0.50	0.7–2.0 ng/mL	12 wk	Not on ACE-I In sinus rhythm	Patients withdrawn from digoxin showed deterioration of EF and exercise capacity on treadmill but no effect on NYHA class or 6-min walk distance. Reduced frequency of worsening CHF with digoxin
Packer et al,[22] 1992	Withdrawal parallel	178	0.125–0.50	0.9–2.0 ng/mL	12 wks	EF <35% NYHA I-III All on ACE-I	Significant favorable effect on treadmill exercise capacity, 6-min walk test distance, EF, and frequency of worsening CHF with digoxin
Drexler et al,[23] 1992	Parallel	133	0.25	?	1 year	mean EF = 53% NYHA II-III No diuretics or ACE-I	Improved quality of life and NYHA class with digoxin

*Digitoxin used.
ACE-I = angiotensin converting enzyme inhibitors. CHF = congestive heart failure; EF = ejection fraction; NYHA = New York Heart Association.

fraction <0.40 and 85% of patients had New York Heart Association (NYHA) class I-II heart failure. After 6 months, there was a favorable nonsignificant improvement in exercise time in the digoxin group compared with placebo, and ejection fraction increased by 4.1% in the digoxin group vs 1.3% in the placebo group ($p < 0.05$). Eight patients given digoxin and 19 given placebo had to be hospitalized due to CHF. There were 7 deaths in the digoxin group and 6 in the placebo group. In the xamoterol-digoxin trial,[18] 204 patients were randomized to receive digoxin or placebo; 80% were in NYHA class I-II. A fixed dose of 0.25 mg digoxin/day was administered. In patients who completed the 3-month double-blind phase, there was no difference in exercise duration between treatment groups. There was no difference in symptoms between groups, although decreases in peripheral edema and rales were found among digoxin-treated patients. No deaths occurred in the digoxin group compared with 1 in the placebo group. In the milrinone-digoxin trial,[19] 111 patients were randomized to receive digoxin or placebo. After 3 months, ejection fraction increased by 1.7% in the digoxin group and decreased by 2% in the placebo group ($p < 0.01$). Exercise tolerance in patients receiving digoxin increased by 14% compared with those given placebo ($p < 0.05$). Three patients in the digoxin group and 4 in the placebo group died during treatment. None of the trials just mentioned reported a preferential benefit in any particular subgroup. In another multicenter study,[21] 133 patients with documented myocardial infarction resulting in regional wall motion abnormalities and mild heart failure were randomized to digoxin or placebo. Most patients had little impairment of ejection fraction. After 1 year of treatment, digoxin resulted in improvement in quality of life and NYHA class compared with the placebo group ($p < 0.05$). No differences in exercise tolerance were observed.

The results from 2 parallel trials of digoxin withdrawal versus placebo were recently reported.[22,23] In a study of 88 heart failure patients in sinus rhythm who were not on ACE inhibitors, Young et al[22] reported that patients withdrawn from digoxin showed deterioration of ejection fraction and exercise capacity on the treadmill. However, digoxin withdrawal had no effect on NYHA class or the 6-minute walk test. In a larger study of 178 patients with a low ejection fraction and on ACE inhibitors, Packer et al[23] reported a significant favorable effect of digoxin on ejection fraction, exercise capacity on the treadmill, the 6-minute walk test, and the frequency of worsening of CHF, compared with the placebo group.

Although there have been a large number of randomized trials conducted to evaluate the effect of digoxin, these trials have had several limitations. First, all of these trials except one have been withdrawal trials; therefore it would not be possible to evaluate the impact of initiation of digoxin compared with placebo. Second, none of these trials was of sufficient size or duration to provide reliable information on mortality. Third, patients with relatively preserved ejection fraction have not been included in most of these trials and therefore extrapolations of the available data are limited. Fourth, patients received concomitant ACE inhibitor therapy in only one of these trials. Therefore, given these limitations, there is still a need for a trial to evaluate the effect of digoxin on morbidity and mortality in a broad spectrum of patients with heart failure and concurrent ACE inhibitor therapy.

TABLE II Summary of Eight Studies Examining the Association of Digoxin Use and Mortality in Postinfarction and Heart Failure Patients Given Digitalis

Reference	Mortality Risk
Postinfarction studies	
Moss et al,[24] 1981	Higher mortality among patients on digoxin overall, but differences compared with those not on digoxin not significant. Statistically significant excess in retrospectively identified subgroup of patients with heart failure and complex VPDs. This subgroup comprised only 8.4% of total population
Bigger et al,[25] 1985	Nonsignificant higher mortality with digoxin overall and in the subgroup identified by Moss et al[21]
Sweeney et al,[26] 1991	Significant excess in sudden death in group receiving digitalis. Overall mortality not provided
Ryan et al,[27] 1983	Nonsignificant higher mortality with digoxin overall and in several subgroups examined
Byington and Goldstein,[28] 1985	Nonsignificant higher mortality with digoxin overall and in several subgroups examined
Muller et al,[29] 1986	Nonsignificant higher mortality with digoxin overall
Madsen et al,[30] 1984	Nonsignificant higher mortality with digoxin overall and in several subgroups examined
Heart failure studies	
Mancini et al,[31] 1984	High serum digoxin levels associated with significant increase in mortality after adjustment for various risk factors
Sackner-Bernstein et al,[32] 1991	Nonsignificant higher mortality with digoxin overall

VPD = ventricular premature depolarization. Nonsignificant refers to a comparison not achieving statistical significance.

EFFECT OF DIGITALIS ON MORTALITY

The effect of digitalis on survival among patients following myocardial infarction or with heart failure has been analyzed by several investigators using existing data bases.[24–32] As shown in Table II, several studies suggested that digitalis might increase the risk of sudden death or mortality among subgroups of patients with frequent ventricular ectopy. In some of these studies,[26,31] digitalis use was associated with a significantly higher risk of death compared with those not using digitalis, after adjustment for differences in risk factors. However, other studies suggested that the higher mortality seen among digitalis-treated patients was largely due to a higher incidence of adverse risk factors. In these studies, after statistical adjustments, the apparently higher mortality associated with digoxin use was not statistically significant.

A critical review of these studies indicates that the effect of digitalis on survival cannot be assessed reliably by retrospective analyses of data bases, but rather requires large, randomized, controlled trials.[33] In this context, it is worth noting that an

TABLE III Overview of Mortality Among Phosphodiesterase Inhibitors and β Agonists

	No. Deaths/Total No. Patients				
Agent/Trial	Active	Control	Odds Ratio	95% CI	p Value
Phosphodiesterase inhibitors (PDEI)[35]	67/642	35/482	1.58	1.04, 2.41	0.03
PROMISE[36]	169/562	126/526	1.36	1.04, 1.78	0.04
Subtotal for all PDEI	236/1,204	161/1,008	1.39	1.11, 1.74	0.01
β agonists*[35]	55/810	17/424	2.07	1.23, 3.49	0.001

*Includes xamoterol, which has both β agonist and antagonistic effects.
CI = confidence interval; PROMISE = Prospective Randomized Milrinone Survival Evaluation.
Adapted from *Circulation*.[35]

overview of all randomized trials with inotropic agents other than digitalis shows excessive mortality with each class of agent and, overall, a 2-fold excess death rate in treated versus control patients ($p < 0.001$).[34] Table III notes this adverse effect of nondigitalis inotropic agents has been observed with dobutamine, a β agonist, milrinone and enoximone, both phosphodiesterase inhibitors, and xamoterol, a β agonist with β-blocking properties.[35,36] These data may arouse concerns that an increase in mortality is also possible with digitalis. It should be borne in mind, however, that most nondigitalis agents work through the cyclic adenosine monophosphate mechanism, whereas cardiac glycosides like digoxin work via a cell-membrane inhibitory effect on the ion exchange pump. The latter enhances contractility, presumably by inducing shifts in intracellular calcium.[37]

All the data base studies of digoxin that came to apparently contradictory conclusions were based on retrospective analyses of data collected primarily for other purposes, rather than data from randomized trials. Since such methods also have moderate inherent biases, they are generally not capable of evaluating reliably whether digoxin has a moderate beneficial or harmful effect on mortality. Therefore, based on currently available data, it is completely uncertain what effect digitalis is likely to have on mortality.

It is quite possible that digitalis-induced improvements in ejection fraction and exercise tolerance may be associated with less deterioration of clinical status, fewer hospitalizations for worsening CHF and fewer deaths due to progressive CHF. Another likelihood is that its positive inotropic effects are of secondary importance, and its actions on the autonomic nervous system are either of primary or equal importance. In addition to vagal enhancement, there is augmented baroreceptor reflex sensitization and reduced sympathetic outflow. For example, there is an increase in forearm blood flow, a reduction in venous tone and acute inhibition of renin, angiotensin and aldosterone output. On the other hand, equivocal and small improvements in ejection fraction, exercise tolerance, or both, as well as alteration of autonomic function, may not be associated with reduced mortality. Further, digitalis has been shown experimentally to increase infarct size and to reduce the threshold for the development of ventricular fibrillation and ventricular tachycardia in myocardial infarction.[38,39] The tendency toward an increase in arrhythmias may be potentiated by hypokalemia or coexisting ischemia. Another issue is depression; reports of depression associated with digitalis use following myocardial infarction have appeared sporadically over the past 2 decades.[40,41] Therefore, there are theoretical reasons to expect digitalis to have a beneficial effect on some outcomes and harmful effects on other outcomes. At present, the balance between the potential for benefit and that for harm is impossible to estimate without a large randomized trial.

Even a moderate effect on mortality would have substantial public health and medical importance. A trial that showed a reduction in mortality of perhaps 10% or 20%, for example, would appropriately encourage widespread use of digoxin. If, however, the trial showed that treatment had no detectable effect on mortality or major morbidity, the numbers of patients receiving the drug would decline. Moreover, even if digoxin were shown to increase the risk of death by only 10% or 15%, it might prove to be responsible for 10,000 to 15,000 premature deaths annually in the United States alone. A trial that clearly demonstrated such an adverse effect would lead to a major reevaluation of the role of digoxin. In addition to determining the effects of digoxin on mortality, it would be important to assess its effects on morbidity (e.g., hospitalization) and quality of life. For example, if digoxin had a neutral effect on mortality but reduced the number of hospitalizations or improved quality of life, it would still be considered clinically useful.

DESIGN OF A LARGE TRIAL OF DIGOXIN IN HEART FAILURE

A large randomized trial to evaluate the effects of digoxin on mortality is being sponsored by the National Heart, Lung, and Blood Institute in conjunction with the Department of Veterans Affairs Cooperative Studies Program. The primary aim of this study is to determine whether digoxin

as beneficial, harmful or no effects on total
ortality among 7,000 patients with clinical heart
ailure who are in sinus rhythm and have moderate
r severe impairment of left ventricular systolic
unction (ejection fraction ≤ 0.45). The diagnosis
f clinical heart failure is based on current or past
vidence of low cardiac output (e.g., limitation of
ctivity) or congestion (edema, elevated jugular
enous pulse, rales or radiologic evidence of pulmo-
ary congestion). Patients with an ejection fraction
>0.45 (expected number of 500 to 1,000 patients)
ill be entered into a parallel but separate ancil-
ary study. Patients will be randomized to receive
igoxin or placebo in addition to other standard
herapy (i.e., ACE inhibitors, diuretics, other va-
odilators). The study also will assess the effects of
igoxin on cardiovascular mortality, deaths due to
rogressive heart failure, deaths presumed to be
ue to arrhythmias, hospitalization for worsening
eart failure and several other causes, including
igoxin toxicity and arrhythmias; and quality of life.
he effects of treatment on mortality and other
utcomes will also be evaluated in subgroups based
n ejection fraction, heart size on chest radio-
raph, etiology, previous use of digoxin and base-
ne NYHA classes.

More than 300 hospitals in Canada and the
Jnited States have agreed to participate. The
tudy started recruiting patients in early March
991, and the rate of recruitment has been gradu-
lly increasing and is now between 330 and 350
atients per month. By the end of May 1992,
$>4,200$ patients had been randomized from about
50 hospitals. Recruitment is scheduled to be
ompleted by December 1993, and all patients will
e followed for a further 2 years. The results are
xpected to become available in 1995 or 1996.

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DISCUSSION

Dr. Creager: What is your rationale for including patients with ejection fractions (EFs) >0.45 in your randomized trial of digoxin in heart failure?

Dr. Yusuf: If the effect of digoxin is at least to some degree mediated through factors independent of inotropism, e.g., an effect on the baroreflexes, then one might expect an effect in these patients. Suppose we only study patients with low EFs. Then we would have to either extrapolate our findings to patients with higher EFs or perform another study to find out the effects of digitalis in these patients.

Dr. Creager: Do these patients with preserved EF have restrictive cardiomyopathies, heart failure secondary to mitral stenosis or right-sided heart failure secondary to cardiovascular disease? Have you defined this group?

Dr. Yusuf: Yes, we have. Patients with severe uncorrected valvular problems are not included in this group. We do have documentation of the primary and secondary etiologies from the patients' physicians. About 50% of our group of patients with EF >0.45 has ischemic heart disease. Patients with restrictive cardiomyopathies, amyloid or mitral stenosis are excluded.

Dr. Packer: We participated in an analysis of prognostic factors in the PROMISE trial. We took all of the baseline variables that were measured in that trial and determined whether they were univariate predictors of mortality. Then we created a model to see which were independent. It turned out that the serum digoxin concentration was, when adjusting for all other variables, an independent predictor of mortality. The higher the serum digoxin concentration, the higher the mortality, and this was independent of EF, arrhythmias, every severity of heart failure. The one thing we did not and could not adjust for, however, was the fact that PROMISE was a noninvasive study. So we did not measure invasive hemodynamic variables.

Then we went back to our own data base of invasively monitored patients. When we took the invasive measurements out of our model, serum digoxin concentration was an independent predictor of mortality. When we put the hemodynamic variables back in, it was no longer an independent predictor. The implication is that you cannot completely adjust for all variables, because you cannot possibly measure everything.

Dr. Yusuf: I fully agree with you. But adjustment is totally appropriate for most of our interventions, where the effect is either moderate or small to nonexistent. The effect of penicillin on pneumococcal pneumonias is so large that one does not need a trial nor does one have to adjust. At the other end, when the effects are small, adjustments probably will not help detect an effect.

Dr. Mancia: I think it takes a lot of courage to do these studies because there are a very high number of complex factors one cannot control.

Dr. Yusuf: That is exactly why one does randomized trials. If such trials are large all important prognostic factors tend to equalize between the 2 groups.

Redefining the Role of Digoxin in the Treatment of Atrial Fibrillation

Brian H. Sarter, MD, and Francis E. Marchlinski, MD

Atrial fibrillation (AF) encompasses a variety of discrete clinical syndromes, including paroxysmal, chronic, acute, and postoperative. Digoxin, long considered the mainstay of therapy for rate control in all types of AF, appears to have only modest electrophysiologic effects, which are mediated primarily by the autonomic nervous system. Digoxin has less potency than the calcium antagonists or β-blocking drugs with respect to atrioventricular nodal blockade. Although less potent than calcium antagonists or β-blocking drugs on the atrioventricular node, digoxin provides positive inotropic support, whereas the other 2 agents can suppress left ventricular function. Thus, digoxin is the agent of choice in patients with AF in the setting of significant left ventricular dysfunction. However, in the absence of left ventricular dysfunction, digoxin should be considered second-line therapy for the treatment of all AF syndromes.

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For >200 years, digitalis preparations have been used to slow the rapid ventricular response in patients with atrial fibrillation (AF). In fact, treatment of AF was essentially synonymous with institution of digitalis therapy. Over the last 25 years, 3 major developments have mandated a reassessment of the use of digoxin in patients with AF. First, careful study of digoxin's mechanism of electrophysiologic action has demonstrated that the effects on the atrioventricular (AV) node are primarily mediated by the autonomic nervous system[1]; thus, digoxin will be less efficacious in slowing the ventricular response to AF in clinical situations associated with increased catecholamines. The second is the recognition that the autonomic, electrophysiologic, and neurohormonal milieu associated with AF varies markedly from patient to patient. For example, acute AF in the setting of the Wolff-Parkinson-White syndrome, paroxysmal AF in the middle-aged hypertensive patient, and chronic AF in the setting of marked left ventricular dysfunction are each discrete syndromes. As will be discussed, treatment with digoxin is appropriate only for the patient with chronic AF in the setting of left ventricular dysfunction in the examples provided. Third, β-blocking and many of the calcium antagonist agents that are now available for clinical use have very potent AV-nodal blocking effects and, unlike digoxin, maintain their potency to some degree despite significant changes in autonomic tone.[2,3] This potency increases their value in the management of selected patients with AF.

This article will review the electrophysiologic effects of digoxin and discuss its efficacy in clinically discrete AF syndromes. We will also compare digoxin with calcium antagonists and β-blocking drugs that are known to affect AV nodal conduction and discuss combining calcium antagonists or β-blocking drugs with digoxin therapy. Finally, we will provide guidelines for the continued use of digoxin in the treatment of AF and suggest the major areas in which additional clinical investiga-

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tion is warranted to further define digoxin's place in the management of patients with AF.

CELLULAR AND ELECTROPHYSIOLOGIC PROPERTIES OF DIGOXIN

Digoxin binds to the sodium–potassium-adenosine triphosphatase (Na^+,K^+-ATPase) transport enzyme.[4] This ubiquitous enzyme transduces the energy derived from ATP hydrolysis to active Na^+ and K^+ transport across the cell membrane against their respective electrochemical gradients. Digoxin binds to the α subunit of the Na^+,K^+-ATPase, causing inhibition of its activity and accumulation of intracellular Na^+.[5] This in turn results in elevated intracellular Ca^{2+} via a Na^+–Ca^{2+} exchange system.[5,6] Although the exact mechanism for this exchange is not entirely clear, it is believed that the energy required for extrusion of intracellular Ca^{2+} is derived from Na^+ moving intracellularly down its electrochemical gradient.[4,5] Thus, as the concentration of intracellular Na^+ increases, the gradient driving Na^+ into the cell diminishes and less energy is available for Ca^{2+} extrusion. It is precisely this elevation of intracellular Ca^{2+} that is thought to account for digoxin's positive inotropic effects.[4–6] Unfortunately, the mechanism or mechanisms responsible for digoxin's electrophysiologic effects are somewhat more complex.

Digoxin's predominant electrophysiologic effects are mediated indirectly via the autonomic system and to a lesser extent through a direct effect on cardiac tissue.[1,5,7] The predominance of these effects depends on the dose of drug, type of cardiac tissue and baseline autonomic tone. Most of digoxin's effects at therapeutic concentrations are due to its interaction with the autonomic nervous system. At therapeutic concentrations of the drug, vagal tone is enhanced. Digoxin acts on several components of the parasympathetic nervous system both centrally and peripherally. Various studies examining the carotid sinus and aortic arch indicate that digoxin causes excitation of the baroreceptors in these tissues.[1] Other studies suggest that digoxin may sensitize the autonomic ganglion to acetylcholine, directly improving ganglionic transmission.[8] There is also evidence to suggest that digoxin potentiates end-organ responsiveness to acetylcholine.[1] The sum of these effects is enhancement of vagal tone. Digoxin's effect on the sympathetic nervous system is less apparent. Some data suggest that digoxin has an antiadrenergic effect at therapeutic levels.[8] However, as drug levels approach toxicity, efferent sympathetic discharge in the central nervous system is increased, resulting in release of catecholamines.[9] This increase in sympathetic tone may contribute to digoxin's toxicity.

The various types of cardiac tissue respond differently to digoxin. At therapeutic levels, the effect of digoxin is most potent on AV nodal tissue with minor effects on atrial tissue.[9] His-Purkinje and ventricular tissue are relatively unaffected until levels approach toxicity. Therefore, we will focus on digoxin's effect on atrial and AV nodal tissue.

Information concerning digoxin's electrophysiologic effects in humans is limited by the lack of clinical studies and the difficulty in separating the direct from the indirect effects of digoxin. Much of the assumed electrophysiologic effects in humans has been inferred from results of more basic investigation. In addition, the various clinical studies that have been performed have yielded conflicting results. Engel and Gonzalez,[10] studying the effect of ouabain in humans, showed an increase in atrial effective and functional refractory periods and an inconsistent effect on atrial conduction. Mendez and Mendez,[7] using innervated and denervated canine hearts, found that cardiac glycosides decreased the refractory period of atrial muscle when vagal innervation was intact but increased atrial refractoriness in the denervated heart. Goodman et al[11] studied the effects of digoxin in intact human hearts and postcardiac transplant patients whose hearts were denervated. They found no significant change in the atrial effective or functional refractory period after digoxin administration in either innervated or denervated hearts. The conflicting data suggest that digoxin has minimal, if any, measurable electrophysiologic effects on the human atria at therapeutic serum concentrations.

Digoxin exerts its most marked electrophysiologic effect on the AV node. It prolongs AV nodal refractoriness and slows AV nodal conduction. Prolongation of AV nodal refractoriness was not seen in cardiac transplant patients after acute intravenous digoxin administration.[11] This would suggest that the indirect effect of digoxin predominates in intact hearts. However, Ricci et al,[12] studying the effects of long-term digoxin administration in cardiac transplant patients, found that AV nodal refractoriness was in fact prolonged. Canine studies suggest that denervation results in abolition of the prolongation in AV nodal refractoriness caused by digoxin.[13] These data suggest that prolongation of AV nodal refractoriness is due predominantly to digoxin's effect on augmenting vagal tone with a lesser antiadrenergic or direct effect. This limited direct electrophysiologic effect is important to recognize because digoxin will not cause significant rate slowing in AF that is either a cause or an effect of increased sympathetic tone.

DIGOXIN FOR TREATMENT OF PAROXYSMAL ATRIAL FIBRILLATION

The use of digoxin for the treatment of paroxysmal AF has been recommended, despite lack of evidence of its efficacy.[14–16] The aim of therapy is 2-fold: to prevent the paroxysms from occurring and to control the ventricular response during the episode. There is no evidence to date that digoxin is helpful in achieving either of these goals. Rawles et al[17] recently reviewed 139 episodes of paroxysmal AF identified on Holter monitor recordings and failed to find a beneficial effect of digoxin. The mean ventricular rate at the start of all paroxysms of AF was similar regardless of the presence or dose of digoxin. In addition, patients taking digoxin had more prolonged episodes of AF (defined as ≥ 30 minutes). A smaller study by Gulan et al[18] also failed to show effective rate control with digoxin therapy in 13 patients with paroxysmal AF. Both of these studies are limited in that they examined patients who were already receiving digoxin. Digoxin therapy may have been instituted because of significant cardiac dysfunction and therefore the patient selection may have been biased. Despite these limitations, the available data suggest that the continued use of digoxin for ventricular rate control during paroxysmal AF cannot be advocated. A randomized, placebo-controlled prospective study is needed to determine if digoxin alters the frequency of paroxysms or the rate of longer episodes. No beneficial antiarrhythmic effects for digoxin have been documented to date in this patient population.

DIGOXIN FOR ACUTE ATRIAL FIBRILLATION

Rapid digitalization has been considered the treatment of choice for patients presenting with new onset AF. Rapid digitalization is frequently performed to facilitate conversion to normal sinus rhythm, despite lack of evidence to support this action. Weiner et al[19] prospectively studied 47 episodes of acute AF treated with rapid digitalization. Reversion to sinus rhythm was seen in 40 of these episodes within 96 hours of instituting digoxin therapy. The investigators suggested that digoxin is effective for converting acute AF to sinus rhythm.[19] A major limitation of this study was the absence of an untreated control group. Falk et al[20] performed a randomized, double-blind trial comparing digoxin with placebo in the treatment of 36 episodes of new onset AF. They found similar rates of conversion to sinus rhythm in the digoxin-treated and placebo groups and concluded that digoxin is not effective in converting AF to sinus rhythm. Of note, patients with moderate to severe congestive heart failure were excluded from this study. The effect of digoxin on acute AF in this subgroup of patients has yet to be determined. Given the absence of benefit in prospective controlled trials, digoxin should not be used in acute AF when the intent is to convert the rhythm to normal sinus rhythm.

If the goal of therapy is to slow ventricular response during acute AF, digoxin may be a reasonable therapeutic option. Falk et al[20] reported statistically significant slowing of ventricular rate in patients who received an oral loading dose of digoxin during acute AF. This slowing, however, did not occur until 5.5 hours after administration of the initial digoxin dose. Whether this prolonged onset of action is due to digoxin's weak electrophysiologic effects or to the route of administration is unclear. Serum drug concentration has been shown in healthy volunteers to increase most rapidly after intravenous digoxin administration.[21] Prospective controlled trials are needed to determine if digoxin administered intravenously will achieve more rapid control of ventricular response in acute AF.

DIGOXIN AND CHRONIC ATRIAL FIBRILLATION

Digoxin is commonly prescribed to control ventricular rate in patients with chronic AF. Often, measurements of resting heart rates are used to assess adequate "digitalization." Since the goal of therapy should be to control heart rate and increase work capacity in active patients, assessment of resting heart rates may be inadequate to guide therapy. Although digoxin appears to control resting heart rate effectively, its ability to control ventricular response during exercise is limited. Interestingly, there have been relatively few controlled trials examining the effect of digoxin during exercise in patients with chronic AF.[22–27] Only 1 of 2 studies of resting versus exercise heart rates in patients with chronic AF has shown a significant effect of digoxin on heart rate during exercise, and then only with high dose therapy (0.5 mg/day) (Table I).[22]

The subgroup of patients with mitral stenosis and chronic AF deserves special mention. These patients develop symptoms as the reduced mitral valve area leads to elevation of left atrial pressure with a concomitant increase in pulmonary capillary wedge pressure. They rely on a prolonged diastolic filling period to maintain near normal left atrial pressure and are particularly sensitive to a heart rate elevation. Although most of the studies listed in Table I included a large proportion of patients with rheumatic heart disease (and presumably mitral stenosis), only 1 has examined patients with mitral stenosis separately.[23] In this study, Ahuja et al[23] found that digoxin resulted in ≥50% subjective improvement of symptoms during exercise in only 30% of patients with mitral stenosis and chronic AF.

TABLE I Resting and Exercise Heart Rate Control by Digoxin in Chronic Atrial Fibrillation

Study	Digoxin Dose (mg/day)	Resting HR (beats/min)		Exercise HR (beats/min)	
		Control	Digoxin	Control	Digoxin
Ahuja et al[23]	0.50	116 ± 11	80 ± 10†	190 ± 10	182 ± 10
Lang et al[22]	0.25	109 ± 31	95 ± 23†	160 ± 24	155 ± 26
Lang et al[22]	0.50	109 ± 91	88 ± 24†	160 ± 24	147 ± 29*

*$p < 0.05$ vs control.
†$p < 0.01$ vs control.
HR = heart rate.

It is evident that assessment of a drug's effects on the resting heart rate alone during AF may mislead the clinician. The ability of digoxin or other AV nodal active agents to control heart rate during daily activity in patients with chronic AF has not been determined. Although the resting heart rate may be well controlled, digoxin has a much more limited effect in preventing rapid ventricular rates when the patient is active. This results in marked exercise intolerance.[22,23] Digoxin therapy alone may be adequate for chronic AF in extremely sedentary patients only.

DIGOXIN AS PREOPERATIVE PROPHYLACTIC AGENT

Cardiac arrhythmias are frequently noted postoperatively in patients undergoing major surgery. Supraventricular tachycardias account for a significant portion of these arrhythmias, particularly in older patients. These tachycardias may result in the absence of preexisting heart disease. Supraventricular tachycardias, primarily AF or atrial flutter, are particularly common after cardiac or thoracic surgery; the reported incidence is 16–48%.[28-30] In light of this high incidence, some clinicians advocate the use of prophylactic antiarrhythmic therapy. Three studies evaluating the efficacy of prophylactic digoxin therapy in high-risk patient populations have reported conflicting results. Juler et al[31] retrospectively examined 563 patients who underwent major thoracic surgery. They found a 5-fold increased incidence of postoperative arrhythmias (predominantly AF or atrial flutter) in patients who received digoxin prophylactically. There was also an increase in postoperative mortality in these patients. Tyras et al[32] found a significant increase in the incidence of supraventricular tachycardias in a prospective, randomized study of 140 consecutive patients undergoing cardiac revascularization surgery and receiving digoxin prophylactically. Of note, 6.6% of the patients in the digoxin group developed signs of toxicity prompting drug withdrawal. In contrast, a prospective, randomized trial of 120 patients undergoing coronary artery bypass surgery demonstrated a significant decrease in incidence of postoperative supraventricular tachycardias in patients who received digoxin prophylactically.[33] Andrews et al[34] recently performed a meta-analysis of prophylactic antiarrhythmic therapy in patients undergoing coronary artery bypass surgery. Their study revealed that digoxin is ineffective in the prevention of postoperative supraventricular arrhythmias. Because of these conflicting study results, no firm recommendation can be made. Nonetheless, given the electrolyte shifts, hypoxia and altered renal function frequently associated with major surgery, the risk of digoxin toxicity is increased. The lack of well-defined beneficial effects and the increased risk of toxicity should discourage the use of digoxin for arrhythmia prophylaxis until more convincing data become available.

THERAPEUTIC ALTERNATIVES TO DIGOXIN FOR CHRONIC, PAROXYSMAL AND ACUTE ATRIAL FIBRILLATION

Beta-blocking and some of the calcium antagonist agents are attractive alternatives to digoxin for the treatment of AF because of their potent AV nodal-blocking effects. Beta-blocking agents prolong AV nodal refractoriness through their antiadrenergic effects. The 3 calcium antagonists commonly used in the United States—nifedipine, diltiazem, and verapamil—have varying degrees of effect on AV nodal conduction and refractoriness. In humans, diltiazem and verapamil significantly slow AV nodal conduction and prolong AV nodal refractoriness. In contrast, nifedipine at therapeutic doses appears to facilitate AV conduction and shorten AV nodal refractoriness.[35] This apparent opposite action of nifedipine can be explained by its potent vasodilating effect, resulting in reflex activation of the sympathetic nervous system. This increased sympathetic tone outweighs nifedipine's weak direct effect on AV nodal tissue.

Table II lists the results of studies comparing

TABLE II Digoxin Versus Calcium Antagonist or Beta-Blocker Therapy in Patients with Chronic Atrial Fibrillation

Study	Drug, Dose (mg/day)	Resting HR (beats/min)		Exercise HR (beats/min)	
		Digoxin	Drug	Digoxin	Drug
Roth et al[26]	Diltiazem, 240	86 ± 12	88 ± 19	170 ± 20	154 ± 25*
Roth et al[26]	Diltiazem, 360	86 ± 12	79 ± 17	170 ± 20	136 ± 25*
Pomfret et al[24]	Verapamil, 240	80 ± 4	81 ± 7	162 ± 14	142 ± 11†
Lang et al[22]	Verapamil, 240	95 ± 23	86 ± 20‡	155 ± 26	122 ± 23‡
David et al[25]	Timolol, 20 to 30	91 ± 19	76 ± 15†	135 ± 23	110 ± 11*

*$p < 0.01$ vs digoxin.
†$p < 0.05$ vs digoxin.
‡Statistical analysis not performed.
HR = heart rate.

the effects of 2 calcium antagonists (diltiazem and verapamil) and the β blocker timolol to digoxin in patients with chronic AF. Importantly, none of these studies included patients with a history of congestive heart failure. In this patient population, β blocking and calcium antagonist drugs as sole therapy had greater effect in controlling peak exercise heart rate than digoxin. Only timolol had a greater effect on resting heart rate. Two of these studies measured work capacity and found that patients had improved exercise capacity while taking verapamil compared with digoxin therapy.[22,24] Lang et al,[22] using bicycle ergometry and the modified Master's step test, showed that more patients reached more advanced stages of exercise when treated with verapamil (240 mg/day), alone or in combination with digoxin, compared with digoxin therapy alone. All seven patients with chronic AF studied by Pomfret et al[24] who reached 80% of their maximum predicted heart rate during exercise testing had significantly higher oxygen consumption rates during treatment with verapamil (240 mg/day), alone or in combination with digoxin, compared with digoxin therapy alone. Nine of 12 patients treated with high-dose diltiazem (360 mg/day) developed side effects, and 5 of 28 patients treated with timolol (20–30 mg/day) were intolerant to the drug, limiting the efficacy of these agents in two studies.[25,26] Of note, all patients who were treated with medium dose diltiazem (240 mg/day) tolerated the medication without any adverse effects.[26] Since relatively large doses of calcium antagonists and β blockers were used in all these studies (Table II), the efficacy and drug tolerance of lower dose calcium antagonists or β-blocking therapy in patients with both preserved and diminished left ventricular function are not known.

No trial has systematically evaluated therapeutic alternatives to digoxin for the treatment of paroxysmal AF. As noted by Rawles et al,[17] paroxysms of AF were twice as likely to occur during the day than at night, suggesting an association between development of AF and increased sympathetic tone. Arrhythmias associated with increased sympathetic tone might be better treated with β-blocking agents. Firm recommendations regarding therapy must await the results of randomized prospective trials evaluating the efficacy of single or combined therapy.

The postoperative patient at risk for developing AF is probably best treated with low-dose β blockade. The development of AF or atrial flutter in these patients appears to be potentiated by the high catecholamine state that occurs after cardiopulmonary surgery. Stephenson et al[36] reported that 10 mg of propranolol administered orally every 6 hours from time of transfer from the intensive care unit was associated with a significant reduction in the incidence of postoperative atrial arrhythmias in patients who had undergone coronary artery bypass surgery. Esmolol, a very short-acting β blocker, should be used if there is concern about adverse effects of the longer acting agents.

As previously discussed, digoxin's effectiveness in controlling ventricular response in patients with acute AF is limited by its delayed onset of action. Intravenous calcium antagonists and β blockers have a shorter onset of action and appear beneficial in this patient population. A double-blind, placebo-controlled trial of 113 patients with acute AF demonstrated that intravenous diltiazem was effective (defined as conversion to sinus rhythm or significant slowing of ventricular response) in 94% of patients studied.[37] The median time from initiation to therapy to maximal decrease in heart rate was 4.3 minutes. Waxman et al[38] gave intravenous verapamil to patients with acute and chronic AF. They found a significant decrease in mean ventricular heart rate in the verapamil group compared with the placebo group and this occurred within 5 minutes of drug administration.

TABLE III Digoxin Alone Versus Combination Therapy with Digoxin in Patients with Chronic Atrial Fibrillation

Study	Adjuvant Drug, Dose (mg/day)	Resting HR (beats/min)		Exercise HR (beats/min)	
		Digoxin	Digoxin + Drug	Digoxin	Digoxin + Drug
Roth et al[26]	Diltiazem, 240	86 ± 12	67 ± 16*	170 ± 20	132 ± 32*
Roth et al[26]	Diltiazem, 360	86 ± 12	65 ± 15*	170 ± 20	121 ± 24*
Pomfret et al[24]	Verapamil, 120	80 ± 14	73 ± 4	162 ± 14	143 ± 10†
Lang et al[22]	Verapamil, 240	95 ± 23	75 ± 20§	155 ± 26	114 ± 19§
David et al[25]	Timolol, 30 to 40	91 ± 19	68 ± 15‡	135 ± 23	94 ± 9‡
DiBianco et al[42]	Nadolol, 87	92 ± 19	73 ± 16‡	175 ± 24	126 ± 25‡
Yahalom et al[43]	Practolol, 300	100 ± 21	78 ± 11†	149 ± 25	105 ± 17‡

*$p < 0.05$ vs digoxin.
†$p < 0.01$ vs digoxin.
‡$p < 0.001$ vs digoxin.
§$p < 0.005$ vs digoxin.

Although there have been no prospective, randomized, placebo-controlled trials investigating the use of β blockade specifically in patients with acute AF, 2 studies examining esmolol in the treatment of supraventricular tachycardias suggest benefit in this setting. Esmolol appeared efficacious (defined as >20% reduction in ventricular rate, reduction in absolute ventricular rate to <100/min, or conversion to sinus rhythm) in 74% and 69% of the patients studied who presented with AF.[39,40] Of note, a significant proportion of the patients in these 2 studies (52%, 83%) who received esmolol were chronically maintained on digoxin.[39,40] Additionally, esmolol appears to have efficacy equal to verapamil in the treatment of acute atrial fibrillation.[41] Thus, the administration of a calcium antagonists or β blocker to patients with acute AF appears to control ventricular response effectively and rapidly.

COMBINATION THERAPY: DIGOXIN PLUS CALCIUM ANTAGONIST OR BETA BLOCKERS

Table III lists the results of several studies examining combination therapy with digoxin and β blockers or calcium antagonists in the treatment of patients with chronic AF.[22,24–26,42,43] The addition of a calcium antagonist or β blocker to digoxin resulted in a significant reduction in resting heart rate in all but 1 of these studies.[24] Exercise heart rate was significantly decreased with combination therapy compared with digoxin alone in every study. Only 1 study included patients with congestive heart failure (New York Heart Association classes II and III).[43] All patients tolerated the addition of practolol to digoxin. Based on the available data, the addition of a calcium antagonist or β blocker appears to produce significantly better rate control in active patients with chronic AF who are already receiving digoxin.

Since calcium antagonists and β blockers alone or in combination with digoxin are effective in the treatment of patients with chronic AF, we should also consider whether digoxin added to calcium antagonists or β-blocker therapy provides additional benefit. Two of the studies listed in Table III examined this issue. Roth et al[26] found improved rate control with combination therapy compared with diltiazem therapy alone. Lang et al[22] found that the addition of digoxin to verapamil therapy resulted in greater rate control at rest and during exercise in 54% of patients with chronic AF. This suggests that combination therapy is more effective than monotherapy. Added benefit might be even more apparent in patients with chronic AF and mild to moderate left ventricular dysfunction. In such patients, large dose calcium antagonists or β-blocking therapy is not possible.

ABSOLUTE CONTRAINDICATIONS TO USING DIGITALIS IN THE SETTING OF ATRIAL FIBRILLATION

Digoxin is contraindicated in certain clinical situations. Patients with asymmetrical septal hypertrophy with dynamic outflow obstruction are particularly sensitive to variations in myocardial contractility.[44,45] As contractility increases, obstruction to left ventricular outflow increases and cardiac output decreases. Digoxin, with its positive inotropic effects, should therefore be avoided. Patients with Wolff-Parkinson-White syndrome and AF associated with rapid ventricular response are at risk for development of ventricular fibrillation due to rapid conduction across the accessory pathway. Digoxin has an unpredictable effect on the ventricular

TABLE IV Indications for Digoxin Use in Atrial Fibrillation

Improve systolic left ventricular dysfunction in patients with acute, paroxysmal or chronic AF
Control resting heart rate during chronic AF
Control resting and exercise heart rates during chronic AF when used in combination with β blockers or calcium antagonists
Produce gradual slowing in ventricular response during acute AF

AF = atrial fibrillation.

esponse during AF in patients with Wolff-Parkinson-White syndrome.[46] In some patients, digoxin may shorten the refractory period of the accessory pathway and facilitate the development of ventricular fibrillation. Because it is impossible o predict which patient will have this response, digoxin should be avoided in all patients with the Wolff-Parkinson-White syndrome, particularly hose who show rapid conduction over the accessory pathway in the control state. RR intervals during AF that are <300 ms identify a patient who may be at particularly high risk.

REDEFINED ROLE OF DIGOXIN IN ATRIAL FIBRILLATION

Table IV lists the clinical situations in which the use of digoxin appears to be efficacious in patients with AF. Patients with AF (acute, chronic, or paroxysmal) and depressed left ventricular systolic function should be treated with digoxin. In this setting, large doses of β blockers and calcium antagonists are not an option. Improvement in contractility with digoxin may also facilitate rate control by decreasing sympathetic tone. Digoxin is also helpful in controlling the resting heart rate during chronic AF. Digoxin may be beneficial when used with other agents such as β blockers and calcium antagonists in the control of chronic AF in he absence of left ventricular dysfunction. Finally, digoxin may be used in patients with acute AF when more gradual control of the ventricular rate s acceptable. More rapid rate control requires the more potent and more rapidly acting calcium antagonists and β-blocking agents.

Additional investigation is required to define further the role and optimum dosing regimen of combination digoxin and calcium antagonists and β-blocking therapy in the treatment of acute AF, especially in those patients with mild or moderate heart failure secondary to left ventricular systolic dysfunction. In addition, a randomized, placebo-controlled prospective study is required to determine if digoxin has any clinical value in the management of paroxysmal AF. Firm recommendations regarding the use of digoxin in these settings cannot be made until such trials are complete.

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DISCUSSION

Dr. Gheorghiade: I think most clinicians will agree that in their experience digoxin controls ventricular rate at rest both in patients with congestive heart failure and in those with normal ventricles who experience atrial fibrillation (AF). However, the time required to achieve acute control may be as long as 24 hours, and this is not acceptable. Nowadays, we like to control heart rate much faster. For rapid control, a β-blocking agent or a calcium antagonist[1] should be used in addition to digoxin.

In terms of controlling rate during exercise, the duration is also important. In the study of Lang et al,[2] what was the difference in exercise duration between the control group and the group receiving digoxin?

Dr. Marchlinski: The difference was not significant in the low-dose group. But at the higher dose (0.5 mg/day), there was a greater lowering in the heart rate and a modest, but significant, increase in exercise duration. However, this has not been substantiated by other investigators.

Dr. Podrid: When digoxin slows heart rate at rest, peak heart rate is not as well controlled with digoxin as it is with other agents. Even when you evaluate different time periods during an exercise test, the peak heart rate is still far greater with digoxin alone than it is when a β blocker or calcium antagonist is added.

The important issue is that most clinicians generally manage patients with AF by considering only resting heart rate, and often digoxin is given if the rate is > 60 beats/min. However, the physician tends to forget about the rate when these patients engage in any activity, even if minimal. The point is that many such patients have uncontrolled heart rates when digoxin is used alone, because with normal activity the rate is far in excess of what it should be.

Dr. Marchlinski: I think the key is to use these drugs as additive agents. You can produce a combined effect that is beneficial.

Dr. Gheorghiade: Do you start with digoxin and add a calcium antagonist or β blocker only if the ventricular response is not controlled, or do you use a β blocker or calcium antagonist first?

Dr. Marchlinski: I think it depends on the patient. In patients with chronic coronary artery disease or cardiomyopathy and lots of left ventricular (LV) dysfunction, I would add low doses of a calcium antagonist or β blocker to digoxin therapy. In patients with normal LV function and in chronic hypertensive patients with minimal LV systolic dysfunction, I would only add digoxin as a last resort after trying to control the heart rate with a calcium antagonist.

Dr. Gheorghiade: When you refer to systolic LV dysfunction, do you have a cutoff point (i.e., ejection fraction ≥40%) for which you use a calcium antagonist alone?

Dr. Marchlinski: I think, in general, it depends on the anatomic substrate with which you are dealing. Typically, patients with mitral valve disease or with hypertensive heart disease are given calcium antagonists or β blockers. In patients with ischemic disease, especially those who have had a big myocardial infarction and have depressed left ventricular function, you tend to shy away from large-dose β blockade or calcium antagonist agents—unless you are using those agents to control anginal-type symptoms—and go with digoxin.

We have been discussing AF as a single syndrome. This is a mistake. There are many AF syndromes. Parameters such as the underlying disease state, the age of the patient, the history of prior infarction and other factors that may affect atrioventricular (AV) nodal conduction—all these should be considered before dealing with the potential consequences of treatment.

Dr. Lewis: I agree. I think it is important to realize that there are patients at high risk with AF in whom digoxin would be the agent of choice. Recent studies may have obscured this point. As a result, a patient with AF and cardiomyopathy or underlying heart disease may report to the emergency department, be treated with an agent like verapamil, and suffer a cardiac arrest. I think we have to make sure we understand that digoxin is the only positive inotrope that controls the ventricular response in AF.

In the old days, when probably relatively more of the patients with AF had underlying heart disease, we would talk about the hemodynamic effects of digoxin in preventing AF, diminishing atrial stretch by its hemodynamic effect. Do you think these effects have any role today?

Dr. Marchlinski: I think hemodynamics play a very important role in selected patients—not in everybody. In some patients you are dealing with an electrophysiologic substrate, and it does not matter what the triggers are because there is always enough electrophysiologic disruption to have the potential for AF. In other patients atrial stretch and various other factors clearly play a role, so that it is really difficult to single out and hold any one factor responsible.

Dr. Mancia: I do not doubt that in patients with AF digoxin in combination with verapamil and diltiazem can effectively control ventricular rate during exercise. Because of the exercise-induced adrenergic activation, even a β blocker combined with digitalis should be effective.

What happens, however, when you have increased vagal tone, such as during sleep? Does the combination of digitalis with verapamil or a β blocker produce an untoward lowering of ventricular rate?

Dr. Marchlinski: The resting heart rate does not seem to be dramatically lowered by the combination therapy.

Dr. Mancia: One group of investigators in Glasgow showed that if you add a β blocker to digitalis in patients with AF, you get a marked decrease in ventricular rate during sleep. This decrease was limited to some extent if digitalis and a β blocker with intrinsic sympathomimetic activity were used. You have to support heart rate during sleep; otherwise, you may have problems.

Dr. Ferguson: How about a patient with acute AF in whom you are going to attempt chemical cardioversion? The traditional teaching has been to block the AV node with digoxin and add a type I agent. Are there any data to suggest that substituting another agent for digoxin—say a β blocker or calcium antagonistr—which would amount to giving two negative inotropic agents, has a worse or better effect?

Dr. Marchlinski: The type I agent you are referring to is procainamide, which generally does not have much of an inotropic effect. It is pretty well tolerated.

Dr. Podrid: The approach has always been to use either digitalis or an AV-nodal blocking agent before using a type I agent in patients with AF. The reason given is that quinidine, as well as procainamide and disopyramide, has mild vagolytic activity, i.e., it negates the effect of the vagus. There is thus a concern that quinidine and the other IA drugs have potential for heart acceleration.

However, it must be remembered that quinidine, procainamide and disopyramide also have direct (although minimal) effects on the AV node that are also important. In bundle of His studies done many years ago,[3] there was no change in AV nodal conduction with quinidine.

Dr. Marchlinski: In the electrophysiology laboratory, if you induce AF in patients and give them procainamide acutely, you will increase their mean heart rate by about 20 beats/min. So you have to ask, if the mean heart rate increases by 15–20 beats/min with the infusion of procainamide, will that result in adverse consequences?

Dr. Podrid: This may be the result of a change in blood pressure, which also occurs when procainamide is infused. With all of the oral type I drugs that I have used to revert AF acutely, I have never seen clinically important rate acceleration, except in the patient who becomes hypotensive as a result of the drug. Although digoxin is often given first, a concern is that digoxin can exacerbate AF in patients in whom the vagus plays a role in the occurrence of AF.

The situation is different with atrial flutter. Because the effect of the type I agent is to slow the rate of flutter, another drug should be used. When the atrial rate is slowed from 300 to 200 beats/min (with 2:1 AV nodal conduction), the degree of concealed AV nodal conduction is reduced and there is the potential for 1-to-1 AV nodal conduction and acceleration of the heart rate response.

Dr. Creager: I am concerned about quinidine and procainamide inducing torsades de pointes. If I had to use another agent with digoxin, which one would be less likely to do that?

Dr. Podrid: Although the initial reports of torsades de pointes during treatment for AF were in patients receiving digoxin and quinidine, Koster and Wellens'article[4] reported this arrhythmic event when quinidine was used alone, indicating that it was quinidine, and not the combination, that caused torsades de pointes. With any of the type IA agents, there is a 0.5–1.0% risk of torsades. Digoxin therapy does not seem to increase this.

Dr. Packer: It is characteristic of people who have heart failure and AF to have an excessive early increase in heart rate during submaximal exercise, which, if high and fast enough, can decrease exercise capacity. You can actually make these patients feel better by blunting the increase in heart rate during submaximal exercise. Digoxin will not block that increase. We have achieved success using very small doses of β blockers. The problem with β blockade is that if you give it too often, the ability of the patient to increase heart rate at maximal exercise will be inhibited. I think the trade-off is such that in someone with mild heart failure and AF, particularly in the presence of a mitral valve prosthesis, β blockers will improve submaximal exercise tolerance. Since most people spend their day doing submaximal exercise, they actually feel better with a little β blockade.

Dr. Gheorghiade: I think we all agree that digoxin given alone may not be sufficient to slow heart rate, particularly during exercise. Adding a low dose of β blocker or calcium antagonist is perhaps the best option, since I cannot think of any contraindications, even in patients with significant LV dysfunction. In my opinion, there are not enough data to conclude that a β blocker or calcium antagonist given alone is safe and cost-effective in controlling the ventricular response in chronic AF, particularly in patients with LV dysfunction.

Dr. Marchlinski: I think there are 2 important exceptions. I would not use digoxin in hypertensive middle-aged men with paroxysmal AF. I am also reluctant to use digoxin in someone with normal LV function who has AF. Initially, I will use a β blocker or calcium antagonist.

Dr. Gheorghiade: When digoxin was compared with medium- and high-dose diltiazem for control of heart rate at rest and during exercise in patients with chronic atrial fibrillation[5] but no CHF, 240 mg/day of diltiazem was comparable to therapeutic doses of digoxin at rest, but heart rate at peak exercise was somewhat higher with digoxin compared with diltiazem (170 vs 154 beats/min). Although a higher dose of diltiazem (360 mg/day) resulted in better control of heart rate, 75% of patients developed side effects requiring a decrease in dose. Unfortunately, this study did not assess exercise performance with digoxin or diltiazem.

Dr. Packer: Electrophysiologically, especially during exercise, which is really quite important, digoxin does not do very much to blunt the increase in heart rate in some patients. I think it is worth exploring more the option of using β blockers and calcium antagonists in lieu of digoxin, especially in patients without significant LV dysfunction.

Dr. Podrid: There are data from Israel on the use of verapamil by itself.[2] First, these authors observed that there is a digoxin-verapamil interaction, similar to that which occurs with quinidine. The investigators evaluated therapy with high- and low-dose digoxin, digoxin and verapamil combined, and verapamil alone in patients with AF and various heart diseases. They found that verapamil and verapamil with digoxin, both produced a significant reduction of heart rate at rest and during exercise. Digoxin alone, regardless of dose, did not reduce exercise heart rate. They concluded that verapamil, with or without digoxin, was superior to digoxin alone for heart rate control.

Dr. Lewis: When you consider cost and side effects, I tend to favor using digoxin and then adding the lowest possible dose of β blocker or verapamil. The latter agents have more side effects than digoxin and are more expensive.

Dr. Marchlinski: Patients without significant structural heart disease who develop AF, especially paroxysmal AF, are increasing in number as we get an older and older patient population. Over the years, such patients have been traditionally treated with digoxin. However no evidence that I could find supports this indication. Indeed, some evidence suggests that we may be doing the wrong thing by lumping all types of AF together and using digoxin for treatment. Now, we have more potent agents that appear to provide some antiarrhythmic effect at a lower dose. More data will be required to confirm these findings, which should help us further clarify the role of digoxin and other agents in the treatment of AF.

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Ventricular Arrhythmia in Congestive Heart Failure

Philip J. Podrid, MD, Richard I. Fogel, MD, and Therese Tordjman Fuchs, MD

The importance of ventricular arrhythmia is based on its association with sudden death. In certain groups of patients, ventricular arrhythmia—primarily runs of nonsustained ventricular tachycardia (NSVT)—is associated with an increased risk for sudden death. Although this relationship has been most often reported in patients with recent myocardial infarction, it has also been recognized in patients with dilated cardiomyopathy, regardless of etiology. Therefore, ventricular arrhythmia is common in patients with CHF due to cardiomyopathy. A number of studies have reported that 70–95% of patients with cardiomyopathy and congestive heart failure (CHF) have frequent ventricular premature beats, and 40–80% will manifest runs of NSVT. Many factors are responsible for ventricular arrhythmia in such patients, including structural abnormalities, electrolyte imbalance, hemodynamic impairment, activation of neurohormonal mechanisms, and pharmacologic therapy. Many studies have reported a high yearly mortality in patients with cardiomyopathy and CHF; >40% of deaths are sudden, most often the result of sustained ventricular tachyarrhythmia. Most studies have noted an association between presence (and frequency) of NSVT and risk of sudden cardiac death in these patients. Unfortunately, other techniques—such as the signal-averaged electrocardiogram and electrophysiologic testing—are not helpful in identifying the individual at risk. Although several drug interventions will reduce mortality from progressive CHF, these drugs have not been shown to reduce sudden death and, indeed, have a variable effect on ventricular arrhythmia. Although NSVT is a marker for increased risk for sudden death, it is uncertain if antiarrhythmic drugs will prevent this outcome. Antiarrhythmic drugs have not been shown to be effective for preventing sudden death, although there are as yet no well-controlled randomized trials. Several studies suggest that amiodarone and β blockers are beneficial, but this requires confirmation. For patients who have been resuscitated following an episode of sudden death due to a sustained ventricular tachyarrhythmia, antiarrhythmic therapy guided by invasive and noninvasive techniques appears to reduce risk of recurrent arrhythmia. However, the response rate to antiarrhythmic agents is low and side effects are common in patients with CHF. Especially important is the increased risk of precipitating CHF and aggravating the arrhythmia being treated. For many such patients who have had serious ventricular tachyarrhythmia, the automatic implantable cardioverter defibrillator may prove a better option. Other drugs used for management of CHF reduce overall mortality, but not risk of sudden death.

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Many advances in the treatment of patients with congestive heart failure (CHF) have resulted in improved survival rates. Consequently, the number of such patients being seen by physicians is increasing. Despite the decrease in mortality, largely due to a reduction in deaths associated with progressive CHF, sudden cardiac death continues to be a serious problem. In the vast majority of patients, the mechanism for sudden cardiac death is ventricular tachyarrhythmia, specifically ventricular tachycardia (VT) or ventricular fibrillation (VF).

A number of studies,[1,2] particularly those involving patients with recent myocardial infarction, have reported a significant association between ventricular arrhythmia, particularly runs of nonsustained ventricular tachycardia (NSVT), and increased risk of sudden cardiac death. This relationship is further strengthened when left ventricular (LV) dysfunction and CHF are present.

It has been observed[3-8] that ventricular arrhythmia and NSVT are particularly frequent in patients

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TABLE I Prevalence of Ventricular Arrhythmia in Patients With CHF

References	No.	With VPBs or Couplets (%)	With NSVT (%)
Huang et al[4]	35	93	60
Wilson et al[5]	77	71	50
Meinertz et al[7]	74	87	49
Maskin et al[8]	35	92	71
Von Olshausen et al[9]	60	95	80
Holmes et al[10]	31	87	39
Chakko, Gheorghiade[11]	43	88	51
Francis[12]	346	81	28
Unverferth et al[13]	69	NA	41
Costano-Nordin et al[14]	55	76	40
Neri et al[15]	65	95	80
Gradman et al[16]	295	36	59
Keogh et al[17]	137	39	41
Overall	1,322	87	45

CHF = congestive heart failure; VPBs = ventricular premature beats; NSVT = nonsustained ventricular tachycardia.

TABLE II Factors Predisposing to Arrhythmia in Patients with CHF

Underlying structural disease—abnormal substrate, diffuse and extensive damage
Electrolyte and pH abnormalities
Potassium
Magnesium
Hemodynamic abnormalities (mechanoelectrical feedback)
LV dysfunction and contraction abnormalities
Myocardial stretch—increased ventricular volume
Increased ventricular pressure
Ischemia
Neurohormonal changes
Renin–angiotensin system
Sympathetic nervous system
Therapeutic interventions
Digoxin
Diuretics
β agonists
Phosphodiesterase inhibitors
Vasodilators
ACE inhibitors

ACE = angiotensin-converting enzyme; CHF = congestive heart failure; LV = left ventricular.

with cardiomyopathy and CHF, suggesting an association with sudden cardiac death in such patients. The presence of ventricular arrhythmia is an important concern in this group, given the increasing number of patients with CHF. The purpose of this review is to discuss the prevalence of ventricular arrhythmia in patients with CHF, factors associated with its occurrence, its prognostic importance, benefits and risks of pharmacologic therapy and the role of nonpharmacologic methods of management.

PREVALENCE OF VENTRICULAR ARRHYTHMIA

Although ventricular premature contractions are commonly observed in normal subjects and patients with underlying structural heart disease, they are particularly frequent in those who have CHF, regardless of etiology. Based on data from a number of studies, almost 80% of such patients have frequent ventricular premature contractions, whereas >40% have runs of NSVT (Table I).[4–17] A number of studies[5,10] have reported that there is no relation between presence or type of ventricular premature contractions and severity of CHF as determined noninvasively by LV ejection fraction or invasively by hemodynamic parameters. It is possible, however, that the frequency of ventricular premature contractions and runs of NSVT in an individual patient are related to hemodynamic factors. Additionally, there does not appear to be a relation between ventricular arrhythmia and etiology of CHF (i.e., ischemic vs nonischemic causes).

A number of factors are responsible for the occurrence of arrhythmia in patients with CHF (Table II). These patients generally have extensive diffuse myocardial damage and fibrosis, which result in significant disparity of electrophysiologic properties within the myocardium, primarily in membrane conduction velocity and refractoriness. This provides the appropriate abnormal substrate for arrhythmogenesis.[18] LV dysfunction and the resulting hemodynamic abnormalities, causing myocardial stretch and an increase in intracardiac pressures, are other factors that increase the potential for ventricular arrhythmia. Dean and Lab[19] have provided evidence in humans for what is termed mechanoelectrical feedback. These authors reported that mechanical changes in the ventricular myocardium associated with CHF, particularly an increase in wall stress and LV dilation resulting from increases in preload and afterload, can alter the electrophysiologic properties of myocardial tissue. This is supported by observations[20] that increased myocardial stretch can cause a shortening of action potential duration (phases II and III), resulting in a shortened membrane refractory period. Additionally, myocardial stretch produces an increase in automaticity due to an increase in phase 4 spontaneous depolarization. Since the loading conditions of the failing ventricle are not uniform, different degrees of LV contraction abnormalities, and hence differences in wall stress, can create further electrical disparity in adjacent tissue, predisposing it to arrhythmia.

CHF activates neurohormonal mechanisms, especially the sympathetic nervous system, circulating catecholamines and the renin-angiotensin system.[21] It has been reported that in CHF patients, norepinephrine levels are markedly elevated and sympathetic neural activity, as measured by direct nerve recording, is increased.[21,22] The sympathetic nervous system and circulating catecholamines can interact with the abnormal myocardium and enhance arrhythmogenesis by all three proposed mechanisms for arrhythmia development: reentry, delayed afterpotentials, and enhanced automaticity.[23,24] Sympathetic denervation of the myocardium and the resulting hypersensitivity to circulating catecholamines can also enhance myocardial inhomogeneity and the amount of electrical dispersion.[25]

In patients with cardiomyopathy and CHF, the underlying disease process disrupts sympathetic nerve fibers, resulting in areas of denervated myocardial tissue.[26] This has been documented[25,26] by scanning techniques using the labeled tracer *meta*-[^{123}I]iodobenzylguanidine, which is specifically taken up by sympathetic neural endings. In patients with cardiomyopathy, myocardial uptake of this tracer is heterogeneous and reduced compared with normal subjects, indicating patches of denervated tissue.[26] Inoue and Zipes[25] reported that infarcted myocardial tissue, which also is denervated as a result of hypoxic damage to sympathetic fibers, demonstrates a hypersensitivity to catecholamines that is measured as a greater shortening of the myocardial refractory period than is observed in the normal myocardium. When circulating catecholamines are elevated, such as in CHF, the amount of electrophysiologic heterogeneity within the myocardium is further enhanced, providing an appropriate substrate for arrhythmia. Stimulation of β_2 receptors by epinephrine causes an increased influx of potassium into the cell and the development of serum hypokalemia, another factor promoting arrhythmia.[27]

Although less well studied, activation of the renin–angiotensin system may also enhance arrhythmogenesis by producing electrolyte shifts and increased vascular and ventricular volume and pressure, producing myocardial mechanoelectrical feedback and, in some patients, ischemia.

Electrolyte disturbances are an important and frequent abnormality that may also provoke arrhythmia in patients with CHF.[28] As indicated, neurohormonal activation may induce electrolyte changes, especially hypokalemia, a possible factor for arrhythmogenesis in a vulnerable myocardium.[29] Diuretic agents, often prescribed for patients with CHF, may cause hypokalemia as well as hypomagnesemia. These electrolyte abnormalities alter the excitability and automaticity of the myocardium, precipitating ventricular arrhythmias.

A substantial number of patients with CHF have underlying coronary artery disease and often overt or silent ischemia. Hypoxia yields anaerobic metabolites, pH changes, and electrolyte shifts, all of which can alter the electrophysiologic properties of the myocardial membrane, including automaticity, conductivity, and refractory periods.[30,31] Since ischemia is not uniform, these changes are heterogeneous and cause a dispersion of depolarization and repolarization—important factors in arrhythmogenesis.

Although ventricular premature contractions and runs of NSVT are frequently observed in patients with CHF, an important concern is their association with ventricular arrhythmias and sudden cardiac death. Total cardiac mortality in patients with CHF is high—approximately 50% in the first year.[2–12] Data from a number of studies suggest that 40% of cardiac deaths are sudden.[5,7,10,11] Although sustained VT or VF is the most frequent mechanism for sudden cardiac death in ambulatory patients, accounting for up to 90% of events, bradyarrhythmias have also been observed. Luu and coworkers[32] reported on 216 hospitalized patients with New York Heart Association (NYHA) class III or IV CHF who were awaiting cardiac transplantation. There were 21 episodes of cardiac arrest, 13 (62%) due to sinus bradycardia, high-degree heart block, or electromechanical dissociation, whereas sustained VT or VF occurred in 8 patients (38%). Patients who experienced a bradycardiac arrest were similar to those who had ventricular tachyarrhythmia with respect to age, LV function, history of sustained or NSVT, treatment with antiarrhythmic drugs, and presence of bundle-branch block or first-degree atrioventricular block. Only a history of prior myocardial infarction, which was present in all 8 patients with VT or VF versus 6 of 13 with bradycardiac arrest, separated the 2 groups. It must be emphasized, however, that this study involved hospitalized patients with end-stage CHF who were awaiting cardiac transplantation. For patients with less serious CHF who are ambulatory, sustained ventricular tachyarrhythmia is the most frequent cause of sudden cardiac death.

Although patients with CHF frequently have spontaneous ectopy and a substantial proportion die of VT or VF, the association with ventricular arrhythmia, particularly NSVT, is still controversial amid conflicting data (Table III)[4,5,7,9–11,13,14,16,17,33] This may be because most studies involve small numbers of patients with various types of heart disease and different degrees of LV dysfunction. Holmes and coworkers[10] reported that among

TABLE III Prognostic Significance of NSVT in Patients With CHF

References	No.	Follow-up (mo)	NSVT Prognosis of SCD
Huang et al[4]	35	34	–
Wilson et al[5]	77	12	–
Meinertz et al[7]	74	11	+
Von Olshausen et al[9]	60	12	–
Holmes et al[10]	31	14	+
Chakko, Gheorghiade[11]	43	16	+
Unverferth et al[13]	69	12	+
Costano-Nordin et al[14]	55	16	–
Gradman et al[16]	295	16	+
Keogh et al[17]	137	10	+
Follansbee et al[33]	19	19	+

CHF = congestive heart failure; NSVT = nonsustained ventricular tachycardia; SCD = sudden cardiac death; – = no; + = yes.

TABLE IV Role of Electrophysiologic Testing in Determining Risk of SCD in Patients with Cardiomyopathy and NSVT

References	No. with Cardiomyopathy	No. inducible (%)	Follow-up (mo)	Prediction
Veltri et al[34]	6	3 (50)	23	–
Sulpizi et al[35]	9	5 (56)	29	–
Das et al[36]	24	8 (33)	12	–
Poll et al[37]	20	1 (5)	18	–
Gomes et al[38]	10	?	30	+
Zheutlin et al[39]	13	7 (54)	22	+*
Buxton et al[40]	18	9 (50)	33	–
Stamato et al[41]	15†	0	19	–
Stevenson et al[42]	72	9 (13)	6	–
Hammill et al[43]	53‡	15§	50	–

*Only noninducibility predictive.
†All had idiopathic cardiomyopathy.
‡Twenty-eight patients had CAD, 25 had idiopathic cardiomyopathy.
§Fourteen patients had CAD, 1 had idiopathic cardiomyopathy.
CAD = coronary artery disease; NSVT = nonsustained ventricular tachycardia; SCD = sudden cardiac death; – = no; + = yes.

20 patients with congestive cardiomyopathy, overall mortality at 1 year was 59% in patients with NSVT versus 11% in those with only simple ventricular premature contractions.

In a prospective study by Meinertz and coworkers[7] involving 74 patients with nonischemic idiopathic cardiomyopathy, 7 patients died of progressive CHF after a mean follow-up of 11 months, whereas 12 patients experienced sudden cardiac death. Those who died of either cause had more abnormal hemodynamic parameters than did the survivors ($p < 0.05$). LV function, however, was similar in patients who died of either CHF or arrhythmia. There was a significant relation between presence and frequency of couplets and runs of NSVT and incidence of sudden cardiac death. Thus, 75% of patients who died suddenly had NSVT documented on ambulatory monitoring, but this was not observed in survivors or those who died of CHF. Unverferth et al[13] and Keogh et al[17] also reported that in patients with congestive cardiomyopathy, complex ventricular arrhythmia (particularly NSVT) significantly increased the risk of sudden death. In the Veterans Administration trial evaluating captopril, digoxin, and placebo,[16] multiple logistic regression analysis of 295 placebo patients demonstrated that the presence and frequency of NSVT (> 10 runs/day) were significantly associated with risk of sudden death ($p = 0.003$) as well as total cardiac mortality ($p = 0.008$). LV ejection fraction was also an independent predictor of sudden cardiac death ($p = 0.06$) and total cardiac mortality ($p = 0.006$), but NSVT had the strongest association with sudden cardiac death.

In contrast, other studies have reported no such relation between ventricular arrhythmia and sudden cardiac death. In one report involving 77 patients with CHF, NSVT on ambulatory monitoring was more common in those with the greatest degree of LV dysfunction and symptomatic CHF.[5] NSVT, however, was not independently associated with sudden cardiac death risk. The investigators concluded that ventricular arrhythmia was not an independent predictor of sudden cardiac death but reflected the extent of heart disease and degree of LV dysfunction.

Patients in whom NSVT is clearly associated with a 2-fold to 5-fold greater risk are those having a recent myocardial infarction associated with reduced LV function.[1,2] In these trials, NSVT and reduced LV ejection fraction were each associated with increased risk of sudden cardiac death, and the poorest survival was among patients with both features. Although many studies have established NSVT as a marker for increased sudden cardiac death risk, it does not reliably identify the individual patient at risk. Other techniques—such as electrophysiologic testing and the signal-averaged electrocardiogram—have provided additional data for risk stratification.

ROLE OF ELECTROPHYSIOLOGIC TESTING FOR RISK ASSESSMENT

Electrophysiologic testing is an established and valuable technique for evaluating and managing patients with serious sustained ventricular tachyarrhythmias. Its role in identifying patients with CHF and NSVT who are at risk for sudden cardiac death, however, remains uncertain and controversial (Table IV).[34–43] Only a few studies, each involving small numbers of patients with CHF of various etiologies, have addressed this issue.

An electrophysiologic study by Gomes and coworkers[38] involved 73 patients with NSVT on ambulatory monitoring, 10 of whom had cardiomyopathy. Twenty patients had induced, sustained monomorphic VT (group 1), and 53 patients had no arrhythmia (group 2). LV dysfunction was more prevalent in group 1, but the number of patients with CHF in each group was not specified. After a 30-month follow-up, mortality in group 1 was significantly higher than in group 2 (32% vs 2%, $p < 0.001$). However, the outcome for patients with LV dysfunction and CHF was not separately reported. Zheutlin et al[39] reported similar results in 88 patients with organic heart disease and NSVT, 23 of whom had cardiomyopathy and CHF. As with the Gomes et al study, there was no separate analysis of this group. Studies by Veltri et al,[34] Sulpizi et al,[35] Das et al,[36] and Poll et al[37] involved only patients with cardiomyopathy and CHF. None of these trials showed electrophysiologic testing to be predictive of an arrhythmic event.

It has been suggested that electrophysiologic testing may be helpful in determining sudden cardiac death risk in patients with an ischemic cardiomyopathy but not in those with nonischemic cardiomyopathy. Stamato and coworkers[41] prospectively evaluated 15 patients who had CHF and NSVT due to a nonischemic or idiopathic cardiomyopathy. Sustained monomorphic VT was not induced in any patient, but noninducibility did not necessarily predict a good survival. The authors concluded that patients with idiopathic, nonischemic cardiomyopathy are different from those with an ischemic etiology, and that electrophysiologic testing has a limited role in the former group. Similar results were obtained by Hammill et al,[43] who performed electrophysiologic tests in 53 patients with cardiomyopathy, CHF, and NSVT. Coronary artery disease was present in 28 patients, and 25 had a nonischemic etiology. Fifteen patients had inducible arrhythmia, 14 of whom had coronary artery disease and only 1 had idiopathic cardiomyopathy. Similar to other studies, inducibility was not predictive of outcome in either group after a 15-month follow-up.

In conclusion, the role of electrophysiologic testing in predicting risk of sudden death in patients with CHF and runs of NSVT on ambulatory monitoring remains uncertain. Although it has been suggested that electrophysiologic testing may be of some use in patients with cardiomyopathy resulting from coronary artery disease (i.e., noninducibility predicts a low risk of sudden cardiac death), the predictive role appears limited and remains indeterminate among those with a nonischemic etiology. Continued investigation with larger patient cohorts will be required to resolve this issue.

ROLE OF THE SIGNAL-AVERAGED ELECTROCARDIOGRAM

Over the past several years, the signal-averaged electrocardiogram has become a useful tool, providing noninvasive assessment of risk for an arrhythmic event, especially in patients having a recent myocardial infarction.[44] A number of investigators have reported that the presence of late potentials is an independent predictor of mortality. Kuchar and coworkers[45] analyzed the role of the signal-averaged electrocardiogram and LV function in predicting arrhythmia in 210 postinfarction patients. After a median follow-up of 14 months, there were 15 life-threatening arrhythmic events. Using multivariate analysis, it was determined that a reduced LV ejection fraction <40% and positive late potentials on signal-averaged electrocardiogram were independent variables of outcome; 34% of patients who had both abnormalities had a life-threatening arrhythmic event. By contrast, such events occurred in 4% of patients in whom neither abnormality was present. It has been recently reported that late potentials are of use in predicting sustained VT but are less helpful in predicting VF.[46]

The role of the signal-averaged electrocardiogram and the presence of late potentials for predicting ventricular tachyarrhythmia or sudden cardiac death in patients with cardiomyopathy, especially those with a nonischemic cause, remains uncertain. Poll et al[47] obtained a signal-averaged electrocardiogram in 41 patients who had nonischemic cardiomyopathy, 12 of whom had a history of sustained ventricular tachyarrhythmia. A group of 59 normal subjects served as a control. Of the patients with cardiomyopathy who had a history of arrhythmia, late potentials were present in 83% compared with only 17% of those with cardiomyopathy and no arrhythmia and 7% of the control group. Itoh and coworkers[48] obtained a signal-averaged electrocardiogram in 80 patients, 40 of whom had previous myocardial infarction, 32 nonischemic cardiomyopathy, and 8 no structural heart disease but who had a history of sustained VT. The patients were divided into 3 groups—those with a history of sustained VT (group 1), those with documented NSVT (group 2) and those without arrhythmia (group 3). Of those with cardiomyopathy, late potentials were present in all group 1 patients, 83%

f group 2 patients, and only 36% of group 3. It ould be pointed out that these studies were trospective and provided no information about e predictive value of late potentials in patients ith cardiomyopathy.

Ohnishi et al[49] studied 100 patients with recent yocardial infarction and 54 patients with nonis- emic cardiomyopathy. As a predictor of sudden eath in postinfarction patients, presence of late otentials had a sensitivity of 100%, specificity of 0%, and predictive accuracy of 60%. In patients ith nonischemic cardiomyopathy, abnormal signal- veraged electrocardiogram had a sensitivity of 00%, specificity of 45%, and predictive accuracy f 52%. The authors suggested that signal-aver- ged electrocardiogram may be of value for risk ratification in patients with nonischemic cardio- yopathy, which is similar to its role in postinfarc- on patients.

By contrast, Middlekauff and coworkers[50] re- orted that late potentials in patients with cardio- yopathy and CHF were not predictive. They udied 62 patients with advanced CHF who were eing evaluated for transplantation. No patient ad a history of sustained ventricular tachyarrhyth- ia. CHF was due to an ischemic cardiomyopathy 40 patients and a nonischemic cardiomyopathy 22. Late potentials were present in 16 patients 0%) with ischemic disease but in only 3 (14%) ith nonischemic disease. There was no associa- on between presence or frequency of NSVT and ositive late potentials. After a mean follow-up of 18 days, 18 patients died of a cardiac cause nnual mortality, 37%), and in 9 death was sud- en (annual rate, 20%). The incidence of sudden eath was 12% in patients with late potentials and 1% in those without this abnormality ($p = 0.73$). he authors concluded that late potentials in atients with cardiomyopathy and CHF are related underlying etiology but are poor predictors of dden cardiac death, regardless of etiology.

In conclusion, the presence of late potentials on gnal-averaged electrocardiogram is associated ith an increased risk of sudden death in patients ith recent myocardial infarction, especially when V dysfunction is also present. Its role in predict- g such risk in patients with cardiomyopathy and HF remains uncertain.

FFECT OF CONGESTIVE HEART FAILURE HERAPY ON ARRHYTHMIA

Since a large proportion of deaths in patients ith CHF are the result of arrhythmia, an impor- nt concern is the effect of drugs used to manage these patients on ventricular arrhythmia and sudden death (Table V). Treatment of CHF involves five classes of agents: direct-acting vasodilators, phosphodiesterase inhibitors, sympathomimetic agents, cardiac glycosides, and angiotensin-converting enzyme (ACE) inhibitors. In assessing the effect of these therapies, some studies have used overall mortality as the primary end point, whereas others have focused on density of ventricular arrhythmia. Unfortunately, only a few studies have specifically addressed sudden cardiac death.

TABLE V Effect of Drug Therapy for Congestive Heart Failure on Ventricular Arrhythmia

Drug	Effect on Arrhythmia
Nitrates	0
Hydralazine	0
Minoxidil	0
Prazosin	0
Amrinone	↑
Milrinone	↑
Sympathomimetic drugs	↑
Digoxin	0
Captopril	↓
Enalapril	↓

Direct-acting vasodilators: Direct-acting vasodilators used for treatment of CHF include nitrates, hydralazine, minoxidil, and prazosin. Data suggest that these drugs used alone do not play an important role in decreasing frequency of ventricular arrhythmia or reducing the incidence of sudden cardiac death.[51,52] Their combined use, however, may help reduce total mortality. In a study involving 642 patients with CHF, patients were randomly assigned to receive therapy with placebo, prazosin, or a combination of isosorbide dinitrate and hydralazine.[53] After an average follow-up of 2.3 years, total cardiac mortality in the hydralazine/isosorbide dinitrate group was significantly reduced by 34% compared with the placebo group, whereas there was no change in the prazosin group. Unfortunately, no data were provided about the effect of these agents on arrhythmia presence or frequency, or about the percentage of death that was due to arrhythmia.

Phosphodiesterase inhibitors: Data regarding the positive inotropic phosphodiesterase inhibitors amrinone and milrinone are more substantial. Packer and coworkers[54] administered oral amrinone to 31 patients with CHF and reported a significant improvement in hemodynamic indices. Cardiac mortality, however, was higher than that observed in comparable studies with other agents. In addition, 13% of patients developed sustained

VT during therapy. Several studies[55,56] have reported that oral milrinone increased frequency of ventricular arrhythmia, including both NSVT and sustained VT. By contrast, Ludmer et al[57] followed 74 patients treated with oral milrinone for a mean of 6 months. There was no change in ventricular arrhythmia frequency in 85% of patients and no patient had a serious arrhythmic event.

In the largest reported study of milrinone, DiBianco et al[58] randomly assigned 230 patients with CHF to therapy with placebo, digoxin, milrinone, or both drugs. Although there was a trend for increased mortality in the milrinone group, this was not statistically significant after adjusting for LV ejection fraction ($p = 0.26$). However, 18% of patients receiving milrinone had an increase in ventricular arrhythmias compared with 2% receiving either placebo or digoxin; this increase was primarily in single ventricular premature contraction frequency, and no patient had an increase in NSVT or developed sustained tachyarrhythmia. Preliminary results of the Prospective Randomized Milrinone Survival Evaluation (PROMISE) trial[59] showed an excess mortality of 30% ($p = 0.028$), primarily due to an increase in arrhythmic death, in patients receiving milrinone compared with those taking placebo.

Sympathomimetic agents: Several sympathomimetic agents have been used for the treatment of CHF, including pirbuterol and salbutamol. Although data are limited, studies involving these drugs have reported an increase in frequency of ventricular arrhythmia during therapy.[60,61]

Cardiac glycosides: Cardiac glycosides have long been used for the treatment of CHF. Although they are effective in improving symptoms and the clinical state of patients, little is known about their effect on arrhythmia or their role in improving survival and preventing sudden cardiac death. Lown and coworkers[62] reported on 143 patients with a history of serious ventricular arrhythmia who received multiple doses of intravenous acetyl-strophanthidin, a short-acting, digitalis-like drug. Approximately 25% of patients had a significant reduction in ventricular premature contractions, 50% had no change, and 25% experienced an increase in frequency and complexity of ventricular arrhythmia. There was no relation between presence or absence of CHF and effect of acetyl-strophanthidin on arrhythmias. In another study from this group,[63] there was no association between the effect of acetyl-strophanthidin on ventricular premature contraction frequency and on LV ejection fraction as determined by radionuclide scanning. The authors concluded that digitalis drugs suppress arrhythmia in some patients, independent of their positive inotropic activity and the resulting improvement in LV function. They suggested that the antiarrhythmic effect may be mediated by the drugs' parasympathomimetic activity.

In the Captopril–Digoxin Multicenter Research Trial,[64] involving 300 patients randomly treated with captopril, digoxin, or placebo, digoxin produced no significant change in mean ventricular premature contraction frequency, which was 63.7/hour before therapy versus 66.0/hour at completion of the study. In the DiBianco et al [58] study involving milrinone, digoxin, and placebo, digoxin produced no significant change in ventricular premature contraction frequency when compared with placebo.

ACE inhibitors: There is a large body of data about the effect of ACE inhibitors on ventricular arrhythmia. In animal studies, captopril had no direct effect on the electrophysiologic properties of the myocardium.[65] In one animal model, however, captopril prevented induction of sustained VT when ischemia was produced by inflation of a balloon catheter in a coronary artery.[66]

In the clinical literature, several studies have examined the relation between therapy with ACE inhibitors and improvement of CHF and ventricular arrhythmia. In the Captopril–Digoxin trial, captopril significantly reduced the number of ventricular premature contractions per hour from 64.7 to 35.3.[64] Using a double-blind design, Cleland et al[67] evaluated arrhythmia in 14 patients treated with captopril or placebo. They observed significant differences between the placebo and captopril groups with regard to ventricular premature contraction frequency (1,897 vs 1,384/24 hours), frequency of couplets (14 vs 8/hour) and runs of NSVT (13 vs 5/hour), respectively. Episodes of sustained VT occurred in 7 patients receiving placebo compared with 4 taking captopril. The investigators have also reported that 20 patients studied had a reduction in ventricular premature contractions while receiving enalapril.[68] Ventricular premature contractions were reduced from 2,140 to 1,268/24 hours, and repetitive ventricular premature contractions were reduced from 4.7 to 3.9/24 hours. Webster et al[69] obtained similar results in 20 patients treated with either placebo or enalapril for 12 weeks. Although ACE inhibitors have a beneficial effect on arrhythmia and reduce mortality due to CHF, their effect on sudden cardiac death mortality has been uncertain.[70] However, the Vasodilator–Heart Failure Trial II (V-

HeFT II),[71] which compared enalapril with hydralazine/isosorbide dinitrate, a combination previously reported to improve survival,[54] recently reported that ACE inhibitors also reduce sudden death mortality.

ANTIARRHYTHMIC THERAPY IN PATIENTS WITH CONGESTIVE HEART FAILURE

Although antiarrhythmic drugs are effective in suppressing all forms of arrhythmia in patients with cardiomyopathy and CHF, their role in preventing sudden cardiac death is uncertain. Unfortunately, only a few trials have randomly administered antiarrhythmic drugs or placebo to patients with NSVT and CHF. Chakko and Gheorghiade[11] randomized 23 patients with cardiomyopathy and ventricular arrhythmia documented on ambulatory monitoring to therapy with either procainamide or quinidine; 20 patients did not receive antiarrhythmic therapy. In follow-up, no apparent benefit was seen in patients receiving antiarrhythmic drugs, although therapy was empiric and not based on arrhythmia suppression. Similar results were reported by Unverferth et al[13] in a group of 69 patients, 24 of whom received antiarrhythmic therapy. As with the previous study, there was no attempt to suppress arrhythmia. Parmley and Chatterjee[72] reviewed the outcome of 26 patients with CHF and NSVT who were treated with procainamide, quinidine, or amiodarone. Although sudden cardiac death mortality was reduced in patients receiving antiarrhythmic drugs, the study was not randomized and the drugs' effects on ventricular arrhythmia frequency were not recorded.

Several nonrandomized studies have reported improved survival in CHF patients with NSVT treated with amiodarone. Hamer and coworkers[73] randomized 34 patients with CHF and no history of sustained ventricular tachyarrhythmia to low-dose amiodarone (200 mg/day) or placebo. The drug significantly reduced all forms of ventricular arrhythmia during follow-up; only 1 patient receiving drug died suddenly versus 5 sudden deaths in the placebo group. Cleland et al[74] prospectively followed 152 patients with CHF for a mean of 21 months. The authors concluded that among the patients receiving amiodarone therapy, survival was prolonged but provided no other details about arrhythmia. Kerin et al[75] prospectively followed 110 patients with structural heart disease, LV dysfunction, and runs of NSVT who received low-dose amiodarone (average, 275 mg/day). Survival at 1, 2, 3, and 4 years was 90%, 85%, 85%, and 80%, respectively. Although there was no placebo group, the results were compared with those obtained in historical controls, in whom survival was poorer. Neri et al[15] also reported that amiodarone therapy reduced sudden cardiac death mortality. By contrast, Keogh and coworkers[17] reported no benefit with amiodarone in patients with significant CHF who were awaiting transplantation. However, similar to other trials, patients were not randomized to drug or placebo.

Although the data are limited, antiarrhythmic drugs appear to be effective in preventing sudden cardiac death in patients with CHF and NSVT who have sustained VT induced with electrophysiologic testing. Wilbur et al[76] performed electrophysiologic testing in 100 consecutive patients with ischemic cardiomyopathy and NSVT documented on ambulatory monitoring. Arrhythmia was induced in 42 patients and an effective agent identified in 20. At 1 and 2 years, the respective incidence of sudden cardiac death was 0% and 11% in these patients, versus 34% and 50% in patients with arrhythmia that was persistently induced despite antiarrhythmic therapy ($p < 0.001$). Among 58 patients without inducible arrhythmia, 1- and 2-year sudden cardiac death incidence was similar to that for drug responders. Unfortunately, there was no control group, since all patients with inducible arrhythmia received therapy.

Electrophysiologic testing has been successfully used for drug selection in patients with CHF and a history of sustained VT or VF. The spontaneously occurring clinical arrhythmia, however, is less often induced in patients with idiopathic cardiomyopathy than it is in those with coronary artery disease, in whom the rate of inducibility is >90%. Naccarelli et al[77] reported that arrhythmia was induced in 13 of 25 patients (52%) with idiopathic cardiomyopathy and a history of sustained VT but in none of 12 patients with NSVT on ambulatory monitoring. Prystowsky et al[78] analyzed the results of electrophysiologic testing in 58 patients with idiopathic cardiomyopathy. Sustained VT had occurred prior to testing in 24 patients and was subsequently inducible in 19 (79%) of the 24. By contrast, only 9 of 19 patients (47%) presenting with cardiac arrest and 8 of 15 (53%) with NSVT had arrhythmia induced.

In patients with inducible, sustained arrhythmia, electrophysiologic testing is useful for guiding drug selection. Poll and coworkers[37] reported on 11 patients with cardiomyopathy and CHF who presented with sustained monomorphic VT, 9 of whom had inducible arrhythmia despite antiarrhythmic therapy. After a mean follow-up of 21 months, 6 patients experienced recurrence and 2 who responded to drug therapy remained free of recurrence. In another study, Poll et al[79] reported on 47 patients with nonischemic cardiomyopathy, 27 of whom had a history of sustained arrhythmia. Each of 13 patients with a history of sustained monomorphic VT had arrhythmia induced during electrophysiologic testing versus only 5 of 14 patients with cardiac arrest. During serial drug testing, arrhythmia became noninducible in only 4 of the 27 patients with sustained arrhythmia (15%), and these 4 were free of recurrence after 18 months. There were 8 recurrences among the remaining 23 patients (35%) who did not respond to drug therapy. Similar results were reported by Rae et al[80] in 38 patients, 20 of whom (53%) had an effective drug identified. Among the 20 responders to treatment, there were no recurrences after a follow-up of 21 months, but there were 5 recurrences (28%) among 18 patients with inducible arrhythmia despite drug therapy ($p < 0.05$).

By contrast, Milner and coworkers[81] reported that in patients with cardiomyopathy and CHF, suppression of arrhythmia by a drug determined to be effective based on electrophysiologic testing did not predict freedom from recurrence. Nineteen patients with idiopathic dilated cardiomyopathy and a history of sustained VT or VF underwent electrophysiologic testing; clinical arrhythmia was induced in 13 patients (68%). Although arrhythmia became noninducible in 9 patients with drug therapy, 5 of the 9 (56%) had a recurrence during a 17-month follow-up. This was similar to the recurrence rate (5 of 10, or 50%) in patients with inducible arrhythmia despite drug therapy.

RELATION BETWEEN RESPONSE TO DRUG AND LEFT VENTRICULAR FUNCTION

When an antiarrhythmic drug suppresses arrhythmia, the recurrence rate of sustained VT or VF in treated patients with cardiomyopathy and CHF is reduced. Unfortunately, it has been observed that the response rate to antiarrhythmic agents, specifically moricizine,[82,83] tocainide,[84] and encainide,[85] is low in this patient population. In a study by Takarada et al[86] response to antiarrhythmic drug was associated with several factors, including presence of repetitive arrhythmia, degree of LV dilation, and severity of interstitial myocardial fibrosis ($p < 0.02$).

Several long-term trials with various antiarrhythmic drugs have reported higher recurrence rates in patients with LV dysfunction, regardless of initial arrhythmia suppression. In a noninvasive study involving 94 patients with a history of sustained VT or VF, Hohnloser and coworkers[87] reported that LV ejection fraction was an independent predictor of both short- and long-term drug efficacy. LV ejection fraction was 29% in patients with arrhythmia not controlled by pharmacologic therapy compared with 42% ($p = 0.017$) in drug responders. After a follow-up of 12.9 months, the arrhythmia recurrence rate was 44% in those with LV ejection fraction <35% versus 16% in those with LV ejection fraction >35% ($p = 0.003$), whereas the incidence of sudden cardiac death was 14% versus 4%, respectively ($p = 0.003$). Similar results with noninvasive techniques were reported by Pratt et al[88] and Lampert et al.[89] In the latter study, predictors of recurrent arrhythmia and sudden cardiac death were history of CHF ($p < 0.018$), presence of third heart sound ($p < 0.05$), a reduced LV ejection fraction ($p < 0.002$), and presence of rales ($p < 0.056$).

Pharmacologic therapy guided by electrophysiologic testing has yielded similar findings. Spielman and coworkers[90] analyzed data retrospectively in 84 patients with sustained VT. Using univariate analysis, investigators concluded the following factors were associated with pharmacologic success: age <45 years ($p = 0.01$), hypokinesis as the only contraction abnormality ($p = 0.01$), absence of organic heart disease ($p = 0.03$), and, most importantly, LV ejection fraction >50% ($p = 0.01$). In a retrospective analysis of 239 patients with sustained VT or VF, Swerdlow et al[91] reported that among the strongest predictors for both sudden cardiac death and total cardiac mortality were a poorer NYHA functional class ($p < 0.001$) and lower LV ejection fraction ($p < 0.034$ for sudden cardiac death and $p < 0.0012$ for total mortality). Severity of heart failure was the strongest independent predictor of total cardiac mortality or sudden cardiac death. A similar association between LV dysfunction and sudden cardiac death was observed by Wilbur et al,[92] who reported a relative increased risk of 2.6 associated with reduced LV ejection fraction ($p = 0.0138$). Patients with no arrhythmia inducible during drug therapy had a better LV ejection fraction (42% vs 30% in nonresponders). Among 32 patients with LV ejection fraction >50%, 94% responded to antiarrhythmic drugs, whereas only 59% of the patients with an LV ejection fraction <30% responded.

RELATION BETWEEN LEFT VENTRICULAR FUNCTION AND DRUG TOXICITY

Antiarrhythmic drugs are more likely to cause side effects in patients with CHF. This is due to an alteration of drug pharmacokinetics that affects plasma drug concentrations, dose requirements, hepatic metabolism, and clearance.[93] Since CHF results in a reduction in the volume of distribution, plasma drug concentrations tend to be higher in patients with CHF. A reduction in kidney and liver perfusion due to CHF produces changes in drug distribution, metabolism, and clearance. A decrease in hepatic enzyme activity further impairs the metabolism of these agents and increases their elimination half-lives.[93] Therefore, the initial dose administered to patients with CHF should be low, with upward dose titration carried out slowly and cautiously to avoid excessive plasma drug levels and toxicity.

Another important concern is the potential for drug interactions, especially in patients with CHF who invariably receive numerous medications. The use of diuretics enhances the predisposition to hypokalemia and low magnesium levels, important factors in arrhythmogenesis. Additionally, hypokalemia may interfere with the actions of the antiarrhythmic drugs and negate some of their properties. Digoxin, commonly administered to patients with CHF, has been reported to interact with a number of antiarrhythmic drugs.[94,95] Antiarrhythmic drugs used in combination with other agents such as calcium antagonists, nitrates, and β blockers may produce hemodynamic effects, resulting in further exacerbation of CHF, hypotension, or conduction abnormalities.

Exacerbation of CHF is a serious complication of antiarrhythmic drug therapy. These agents are negatively inotropic, of particular importance in patients with CHF.[96] Although most frequently reported with disopyramide and flecainide use, CHF also can occur during therapy with other antiarrhythmic drugs. In one trial the overall incidence of CHF was 1.8%, but the incidence was almost 4% in those with a clinical history of CHF.[97] Only 1 of 238 patients (0.4%) without a prior history of CHF had this complication compared with 15 of 167 (9%) of patients with prior LV decompensation ($p < 0.001$). The only factors predictive of CHF exacerbation were previous history of CHF due to systolic dysfunction (LV ejection fraction <35%) and presence of idiopathic cardiomyopathy. Gottlieb and coworkers[98] performed invasive hemodynamic measurements in 21 patients with class III or IV CHF (average LV ejection fraction, 21%) who received a single dose of encainide, procainamide, or tocainide. Measurements were obtained prior to and at 30-minute intervals for 3 hours following drug administration. All 3 drugs caused a decrease in cardiac performance, including cardiac index, stroke volume index, and mean arterial pressure, and an increase in systemic vascular resistance.

Aggravation of arrhythmia, one of the most frequent and serious side effects of antiarrhythmic drug use,[99] is defined as (1) exacerbation of preexisting arrhythmia, (2) occurrence of new arrhythmia, and (3) bradyarrhythmia resulting from sinus or atrioventricular nodal dysfunction. The overall incidence of arrhythmia aggravation is 9% when noninvasive methods are used for drug selection and 18% when electrophysiologic testing is used.[99] In a retrospective analysis, Slater et al[100] reported that the only factors predictive of arrhythmia aggravation were the nature of the presenting arrhythmia and the presence of CHF. Risk was significantly greater in patients with sustained VT or VF than in patients with simple ventricular premature contractions or runs of NSVT (odds ratio, 3.4, $p = 0.01$). Patients with CHF due to systolic dysfunction (LV ejection fraction <35%) were at significantly greater risk than patients without CHF (odds ratio, 2.2, $p = 0.04$). Minardo et al[101] reported that factors associated with the provocation of VF by antiarrhythmic drugs were digoxin use, diuretic administration, and presence of hypokalemia. Although LV function itself was not evaluated, the investigators suggested that presence of underlying CHF increases risk of this complication. Pratt et al[88] evaluated 246 patients with NSVT, 12% of whom had CHF. They reported a significant relation between LV ejection fraction and clinical CHF and provocation of CHF or arrhythmia. These life-threatening complications from antiarrhythmic therapy occurred more frequently in patients with LV ejection fraction <30% than in those with LV ejection fraction >30% (15% vs 2%, $p = 0.005$).

NONPHARMACOLOGIC THERAPY OF VENTRICULAR ARRHYTHMIA

Pharmacologic therapy is the cornerstone of management for patients with ventricular tachyarrhythmias, but other approaches are required for those who are drug refractory or who experience serious toxicity from these agents. Often, these are patients with CHF. Surgery, particularly map-guided endocardial resection, is now an accepted approach. But experience during the past decade indicates that patients with significant heart disease and impaired LV function are poor surgical candidates, since they have high operative mortality and a high recurrence rate, despite successful arrhythmic surgery.[102,103]

The strongest independent predictor of postoperative mortality, including sudden cardiac death,

TABLE VI Antiarrhythmic Drug Therapy in Patients with Congestive Heart Failure

- **Benefits**
  - Eliminate arrhythmia-related symptoms
  - Prevent sudden death (unproven)
- **Risks**
  - Drugs less effective
  - Dose-related side effects more common
    - Blood levels higher at any dose
    - Half-life increased
    - Patient tolerance reduced
  - Greater potential for cardiac toxicity
    - Aggravation of arrhythmia
    - Congestive heart failure exacerbation
  - Adverse drug-drug interactions

is poor systolic function.[104] An important concern in patients with CHF is the diffuse and extensive nature of myocardial damage and the presence of multiple potential areas of reentry and arrhythmogenesis. It is difficult to identify all such areas, which accounts for the poor results of surgery in these patients. Although data on endocardial resection in patients with nonischemic heart disease are limited, the results are poorer when compared with the outcome of patients with coronary artery disease. It has been reported[105] that the best surgical results are achieved in patients with coronary artery disease, a discrete LV aneurysm or discrete areas of myocardial scar, intact LV function, and no CHF.

For the patients with CHF and a diffusely diseased myocardium who have experienced life-threatening ventricular arrhythmia, the automatic implantable cardioverter defribillator (ICD) is an important and highly effective treatment for improving survival.[106] Often, the ICD is preferred in these patients because antiarrhythmic drugs are often ineffective and cause serious toxicity and the role of surgery is limited.

The ICD is associated with an impressive reduction in mortality among patients with significant CHF who have been resuscitated from sudden cardiac death. In a study of 70 patients with LV dysfunction and sustained tachyarrhythmia, Tchou and coworkers[107] reported a 2-year survival with the ICD of 93.4% compared with a projected survival, based on delivery of an appropriate discharge by the ICD, of 60.3%. LV ejection fraction $<30\%$ was present in 25 patients, and their survival was 87.6% versus a projected survival of 56.9%. Similar findings were reported by Fogoros et al[108] in 119 patients with significant LV dysfunction who received the ICD. In patients with LV ejection fraction $<30\%$, 3-year cumulative survival was 67% versus a projected survival of 6% ($p < 0.001$). Similar results were obtained by deMarchena et al.[109]

Based on these studies, it has been suggested that the ICD should be used as a bridge for cardiac transplantation in cardiomyopathic patients at high risk for sudden cardiac death. Luceri et al,[110] however, pointed out that many patients with end-stage CHF may not benefit from the ICD, since the mechanism of sudden cardiac death may be bradyarrhythmia and electromechanical dissociation rather than VT or VF. It may also be ineffective in many patients with NYHA class IV CHF who die of progressive failure.

Another proposed use of the ICD is as prophylactic therapy in patients considered at high risk for sudden cardiac death, including those with poor LV function, clinical CHF, and runs of NSVT on ambulatory monitoring. The ICD has not, however, been evaluated in this capacity in well-controlled randomized trials; such trials are now ongoing.

CONCLUSION

Before evaluating the type and frequency of arrhythmia in patients with CHF and prior to initiating antiarrhythmic drug therapy, the patient should be hemodynamically and metabolically stable. LV function should be optimized, electrolyte abnormalities corrected, and active ischemia treated. Once the patient is stable, arrhythmia often may resolve. If arrhythmia persists, a decision about antiarrhythmic therapy must be individualized, with consideration given to the benefits versus risks of treatment (Table VI). Although antiarrhythmic drugs suppress spontaneous arrhythmia and eliminate related symptoms, there are no data that suggest these agents prevent sustained ventricular tachyarrhythmia and sudden cardiac death. These drugs help prevent recurrence in patients who have experienced sustained VT or VF. Unfortunately, there are substantial risks associated with their use, including cardiac toxicity, other organ toxicity and nuisance and disturbing side effects. Antiarrhythmic drugs are less effective in patients with CHF, often cause serious side effects, and must be administered cautiously, using lower doses with slow upward dose titration.

For many patients who have had sustained VT or VF, use of the ICD may avoid the problems associated with antiarrhythmic drug therapy. However, antiarrhythmic drug therapy may also be required to prevent frequent arrhythmia recurrences or to suppress other arrhythmias that may activate the ICD, i.e., atrial fibrillation or NSVT.

Data have yet to confirm that pharmacologic therapy or the ICD will prevent or prolong life in patients with CHF and NSVT at high risk of sudden cardiac death. Studies are ongoing, and it is hoped that results will be available in the next few years.

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DISCUSSION

Dr. Lewis: Do you think amiodarone is separate from the other agents?

Dr. Podrid: Amiodarone may be a drug we should think of separately because it has a number of other effects in addition to its electrophysiologic actions. It is a noncompetitive β blocker, a calcium antagonist, an α inhibitor, and it contains iodine that interferes with thyroid function, which may be particularly important in treating atrial fibrillation in these patients. Studies with this agent in patients with congestive heart failure, however, have not been well controlled.

I have used amiodarone in patients with cardiomyopathy who have difficult-to-control atrial fibrillation that adversely affects left ventricular (LV) function. Amiodarone has made a major impact in improving hemodynamics and quality of life in these patients by preventing atrial fibrillation. In patients who have had sudden cardiac death, it may not be any better than other drugs; recurrence of arrhythmia is still substantial and there is still some risk of sudden death. The drug has problems with substantial toxicity.

Dr. Lewis: Would you use a defibrillator to resuscitate patients who have had sudden death?

Dr. Podrid: As primary therapy for sudden cardiac death, the defibrillator might be preferable when antiarrhythmic drugs are difficult to use and not effective, simply because the outcome is so much better and you avoid a lot of drug-related complications. However, the fact is that 60–70% of these patients will be receiving antiarrhythmic drugs for therapy of other arrhythmias to prevent frequent recurrence of the clinical arrhythmias.

Dr. Gheorghiade: What is the correlation between hemodynamic abnormalities (i.e., a decrease in cardiac output and an increase in pulmonary capillary wedge pressure) and ventricular arrhythmias? Let's say we obtain a Holter recording in a patient who is asymptomatic but has a very low LV ejection fraction, and the recording shows runs of asymptomatic ventricular tachycardia. Since many of these patients may have a very high pulmonary wedge pressure and low cardiac output, is there any evidence that hemodynamic improvement will result in a decrease in ventricular arrhythmias?

Dr. Podrid: Theoretically, you would think that if you improved hemodynamics and reduced LV stretch pressure, etc., you could reduce arrhythmia. But the few studies that have investigated this have not shown a very good correlation between hemodynamics and presence of arrhythmia.

Dr. Gheorghiade: What do you do for patients who are relatively asymptomatic and on Holter recording show multiple runs of multiform ventricular tachycardia?

Dr. Podrid: I do not think there is a simple or even one answer. When I first started in this field in the mid-1970s, we treated all patients unless side effects from these drugs precluded long-term therapy.

There are several reasons for treatment. One is to prevent sudden death. Another is to improve hemodynamics, which may be adversely affected by such arrhythmias. Suppressing some or all of the runs pharmacologically may improve cardiac output. The tradeoff, of course, is the effect of the drug on LV function.

If the patient is asymptomatic, I think you have to be very cautious. My bias right now is not to treat such patients just because their arrhythmia is documented.

Dr. Packer: Another class of drug besides the β blockers may soon be added to the list of antiarrhythmic drugs in heart failure. Data from the Ventricular Heart Failure Trial II (V-HeFT II) suggest that angiotensin-converting enzyme (ACE) inhibitors reduce sudden death and VT when compared to hydralazine and nitrate therapy.

Dr. Podrid: In the V-HeFT II, it appears that patients receiving enalapril experience less arrhythmia, and this is borne out by much of the literature as well. However, the Second Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS II) in Europe was terminated prematurely because enalapril was associated with an increased mortality in the older population of patients with acute infarction and LV dysfunction, although I do not know any further details.

Dr. Packer: Data from the University of California, Los Angeles (UCLA) suggest that bradyarrhythmias in very sick patients with idiopathic dilated cardiomyopathy can be a common cause of sudden death. Do you agree with that?

Dr. Podrid: I think it can happen. Bradyarrhythmia is certainly a concern and is probably more commonly seen in this group as opposed to any other group. However, I still think that overall ventricular tachyarrhythmia is a more common cause of sudden death in patients with cardiomyopathy. The group of patients awaiting cardiac transplant, the sickest, may be an exception as pointed out by the UCLA group.

Dr. Lewis: In view of the grim picture with the antiarrhythmics, is there any chance of acetyl-strophanthidin making a comeback?

Dr. Podrid: Acetyl-strophanthidin is no longer being produced in this country. In fact, currently there is no short-acting digitalis drug available—even ouabain is no longer available.

Dr. Gheorghiade: Could you comment on the role of hypokalemia and hypomagnesemia in the arrhythmias noted in patients with heart failure?

Dr. Podrid: The literature on magnesium is very confused and there are no good data on the role of magnesium.

The only case in which magnesium has been clearly shown to have an effect is in cases of drug-induced torsades de pointes, where it is very effective. Magnesium is now being reported to have some role in the treatment of atrial fibrillation, but data are still very preliminary.

Dr. Mancia: The ACE inhibitors may have an antiarrhythmogenic effect that is similar to that of the β blockers in CHF. They increase vagal drive slightly but consistently and they reduce sympathetic drive, and part of the action is at the receptor level. If one infuses angiotensin II, responses to norepinephrine are increased at the vascular level, although there is no evidence concerning the heart. However, if we assume that what goes on at the vascular level goes on in the heart as well. . . .

Dr. Podrid: I have no doubt that the ACE inhibitors are important. The fact that data are sparse and only suggestive does not mean that they are not an important therapy. While the majority of available data involve only ventricular premature beat reduction, which is not very important, the drug does have a suppressive effect that suggests that it may have a beneficial role.

Clinical Use of Serum Digoxin Concentrations

Richard P. Lewis, MD

The development of the radioimmunoassay for digoxin by Smith and coworkers in 1969 was a landmark in digitalis therapy. Since then, the complex pharmacokinetics of digoxin have been defined. As a result, the incidence of digitalis toxicity has markedly decreased. To use the digoxin assay properly, however, the relation of this pharmacokinetic parameter to digoxin pharmacodynamics must be known and the limitations of the assay itself understood. Systolic time intervals (STI) are uniquely useful to quantitate the inotropic effect of digitalis preparations. This technique can demonstrate the onset and magnitude of the inotropic effect for both oral and intravenous digitalis administration. By defining the mathematical relation between STI and simultaneous serum digoxin concentrations following intravenous administration of 1 mg digoxin, computer simulations can be made of the effect of dosing changes on blood and tissue concentrations. The serum digoxin assay has technical problems relating to quality control, interference by metabolites, and cross-reactions with endogenous digitalis-like substances. Further, a standard time for measurement following dosing has not been established. Physical activity can significantly alter the serum digoxin concentrations by increasing skeletal muscle binding. Numerous drugs can interfere with digoxin absorption or elimination. Using the serum digoxin assay is the only way to assess these interactions. Computer surveillance (ideally with physician or pharmacist interaction) has been used to monitor digitalis but has not yet gained widespread acceptance. This is clearly a method in need of further testing.

(Am J Cardiol 1992;69:97G–107G)

The determination by radioimmunoassay (RIA) of efficacious and toxic serum digoxin concentrations in 1969 dramatically improved digoxin therapy.[1] The incidence of digoxin toxicity has diminished from 25% to 2%, largely because serum digoxin concentrations within the generally accepted "therapeutic range" have been maintained.[2,3] This knowledge has also allowed a more complete understanding of digoxin pharmacokinetics. Unlike most cardiovascular agents, digoxin has prolonged equilibration of serum and tissue concentrations and has a relatively long half-life. Proper interpretation of serum digoxin concentrations, therefore, requires an understanding not only of digoxin's pharmacokinetics, but also of its pharmacodynamics (relation between serum concentrations and clinical effect).[4] Fortunately, digoxin's inotropic effect can be measured by the duration of electromechanical systole corrected for heart rate (QS_2I) from systolic time intervals.[5,6] The QS_2I has been shown[7] to measure the onset and magnitude of this inotropic effect in humans. The changes in QS_2I directly parallel changes in left ventricular dP/dt_{max} (maximal rate of pressure increase in the ventricle), as measured by a high-fidelity manometer tip catheter (Figure 1).[8]

DIGOXIN PHARMACOKINETICS AND PHARMACODYNAMICS

In previous studies from our laboratory,[7] digitalizing doses of 4 commonly used digitalis glycosides were administered intravenously to normal subjects. The shortening of the QS_2I was measured serially and corrected for the molecular weight of the compound ($\Delta QS_2I/mol$). The response curve was exponential, as would be expected for an agent that binds to a receptor[4] (Figure 2). Of interest, the predicted maximum ΔQS_2I was not significantly different for any of these compounds, thus validating the empirically derived digitalizing doses[7] (Table I).

Exponential curves have a time constant representative of the point at which approximately 66% of peak effect has been attained. By comparing time constants, the relative speed of onset of

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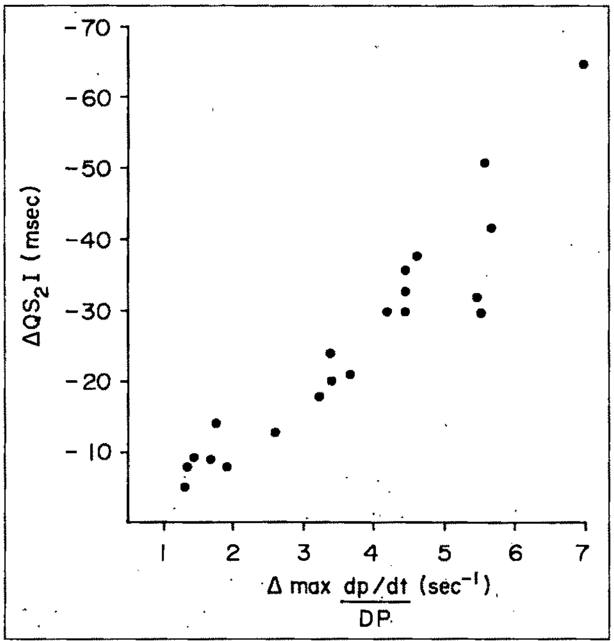


FIGURE 1. Changes (from baseline) in the duration of electromechanical systole corrected for heart rate (ΔQS_2I) and left ventricular dP/dt_{max} (maximal rate of pressure increase in the ventricle) corrected for developed pressure ($\Delta_{max}dP/dt/DP$), obtained serially following administration of 1 mg digoxin intravenously to 5 patients. A high-fidelity catheter system was employed. The direct relation between increased rate of pressure development and shortening of the QS_2I is apparent. (Reprinted with permission from *Cardiovasc Clin*.[8])

activity of the various digitalis compounds can be determined[4,7] (Table I and Figure 2). Intravenous digoxin is an intermediate digitalis formulation in terms of rapidity of onset of action; most of the inotropic effect from an intravenous dose is reached within 60 minutes. Thus, only 1–2 hours need elapse between intravenous digoxin treatments.

In Figure 3 intravenous digoxin's onset of inotropic effect is compared with its onset of slowing heart rate in patients with atrial fibrillation.[4] The atrial fibrillation data are replotted from the original data of Gold et al.[9] Remarkably, the curves are identical. Thus, both the inotropic and chronotropic effects of intravenous digitoxin have similar pharmacodynamics. Others, however, have reported a more rapid effect on atrioventricular conduction in patients with sinus rhythm.[10]

TABLE I Inotropic Response to Treatment with Four Commonly Used Digitalis Glycosides

Digitalis Glycoside	Theoretic Maximum Inotropic Response (QS_2I/mol ± SEM)	Time Constant (min ± SEM)
Ouabain	17.6 ± 4.2	5.8 ± 0.06
Deslanoside	19.5 ± 5.2	7.2 ± 3.3
Digoxin	16.6 ± 4.6	23 ± 2.3*
Digitoxin	15.5 ± 1.8	56 ± 10.0*

*$p < 0.001$ for all pairs.
QS_2I = duration of electromechanical systole corrected for heart rate.
Adapted from *Circulation*.[7]

The onsets of inotropic effect for the oral glycosides digoxin, digoxin elixir, and digitoxin tablets are compared in Figure 4.[4] Given orally, the 3 compounds have a similar onset of action, with peak effect reached at 4–8 hours. The slower onset of pharmacodynamic effect is related to a delay in the absorption of oral compounds.

In Figure 5 the effect of an intravenous digitalizing dose of digoxin on the ΔQS_2I is compared in normal subjects and patients with congestive heart failure (CHF).[4,11] The time course and extent of shortening of the QS_2I are identical for the 2 groups, suggesting that there are no major pharmacokinetic or pharmacodynamic alterations when CHF is present. Although shortening of the QS_2I indicates inotropic stimulation has occurred, it does not necessarily imply a resultant hemodynamic benefit. Improvement in the ratio of subintervals of QS_2I (pre-ejection period/left ventricular ejection time) indicates improved left ventricular contraction occurs in the majority of patients with CHF.[8,11]

To define more precisely the relation between

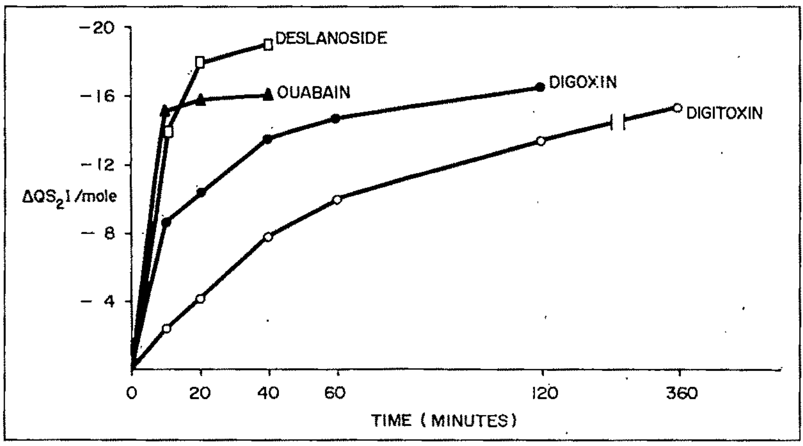


FIGURE 2. Onset of activity of 4 digitalis glycosides administered intravenously. The inotropic response is shown as the change in the duration of electromechanical systole corrected for heart rate (ΔQS_2I) per mole of glycoside. (Reprinted with permission from *Cardiotonic Drugs*.[4])

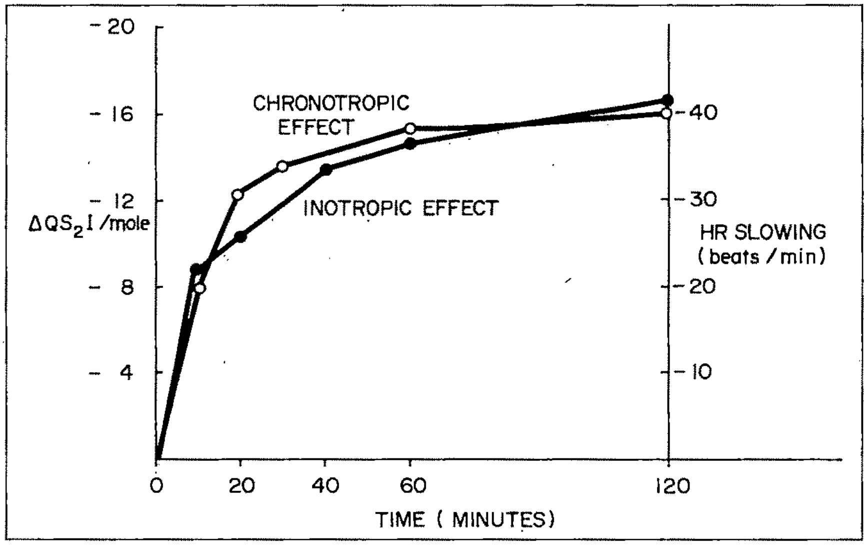


FIGURE 3. Comparison of inotropic and chronotropic effects of intravenous digoxin over a 2-hour period. The chronotropic effect is calculated from the slowing of heart rate in patients with atrial fibrillation and the inotropic effect from the shortening of change in the duration of electromechanical systole corrected for heart rate (ΔQS_2I) per mole. (Reprinted with permission from *Cardiotonic Drugs*.[4])

serum digoxin concentration, tissue digoxin concentration, and digoxin's inotropic effect, we administered 1 mg digoxin intravenously to 10 normal subjects[12]; 22 serum digoxin samples and QS_2I measurements were obtained simultaneously over a 4-day period. The serial digoxin concentrations best fit an open, 3-compartment, pharmacokinetic model noted in a prior study.[13] When the predicted tissue accumulation of digoxin in the deep compartment of this model was correlated with the ΔQS_2I, there was a highly significant, nonlinear relationship[12] (Figure 6). This nonlinear relation is consistent with a finite action for digoxin, and not with earlier theories that had postulated a linear dose-response curve for digitalis throughout the therapeutic range. As will be discussed, the nonlinear relation has major implications for digoxin dosing.

Employing the raw data from the previous study,[12] we were able to make various computer simulations. Figure 7 shows a dose–response curve for the inotropic effect of digoxin in relation to serum concentration.[14] Figure 8 shows the relation between serum digoxin concentrations and tissue concentrations following dosing with digoxin.[15] The peak serum level gradually increases as steady state is approached. More importantly, the more slowly equilibrating tissue concentration shows much less day-to-day variation. This represents the major

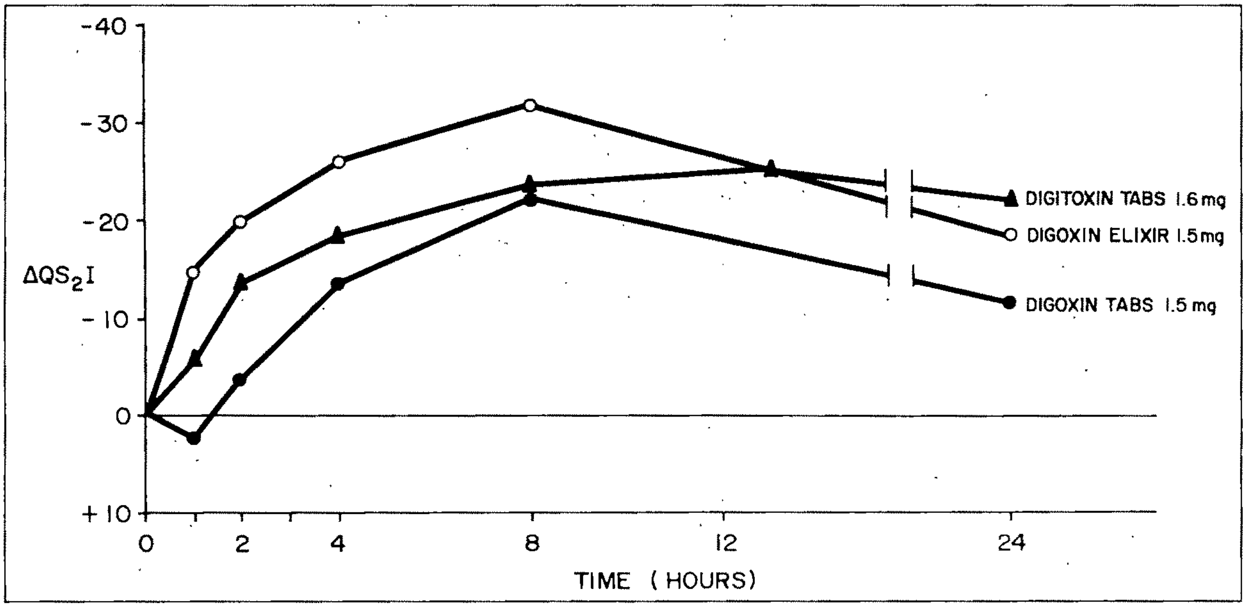


FIGURE 4. Onset of inotropic activity over 12 hours for oral digitoxin tablets, digoxin elixir, and digoxin tablets. Digoxin elixir has the most rapid onset of activity; digoxin tablets have the slowest onset. The lesser effect on the change in duration of electromechanical systole corrected for heart rate (ΔQS_2I) by digoxin tablets represents incomplete absorption. Digitoxin requires up to 12 hours to attain its maximum effect, but its onset of activity is similar to that of digoxin tablets. (Reprinted with permission from *Cardiotonic Drugs*.[4])

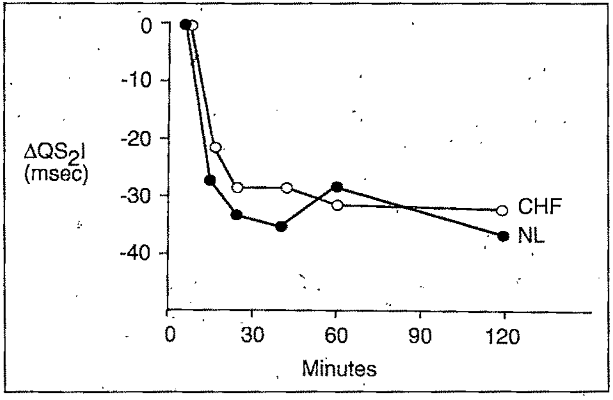


FIGURE 5. Shortening of the change in duration of electromechanical systole corrected for heart rate (ΔQS_2I) in normal subjects (●) versus subjects with congestive heart failure (○) after intravenous administration of 1.6 mg deslanoside. There is no significant difference in onset or extent of shortening. (Reprinted with permission from *Cardiotonic Drugs*.[4])

advantage of an agent with a long half-life. The phenomenon does not occur with most cardiovascular agents, for which rapid changes in serum concentration between dosing are directly manifested as diminishing tissue effect.

Figure 9 depicts the relation between serum digoxin concentration and tissue response for a single dose of digoxin given intravenously or orally.[14] The response is more rapid with the intravenous dose, but at 12 hours there is minimal difference between formulations.

Figure 10 illustrates the difference between starting digoxin with a single daily maintenance dose and using a digitalizing dosage regimen in normal subjects.[14] Although nearly twice as much digoxin was given in the loading-dose protocol, tissue and blood concentration at the end of 96 hours are nearly identical in the 2 dosing groups. Thus, when rapid onset of action is not required, a loading dose of digoxin need not be given. In patients with chronic heart failure, however, renal function is often diminished and the half-life of digoxin is prolonged. Reaching steady state would therefore take up to twice as long in such patients.

Figure 11 illustrates a more rapid decline of the serum digoxin concentration than of tissue effect when digoxin therapy is stopped.[14] In patients with a prolonged serum half-life, the effect is magnified. This observation has clinical implications, for example, when assessing whether an arrhythmia is related to digitalis therapy. It may take several days for the *tissue* digoxin concentration to fall substantially.

Digoxin and digitoxin are the 2 most commonly used cardiac glycosides. Remarkably, these agents differ by only 1 hydroxyl group on the steroid nucleus, but have strikingly different pharmacokinetic properties due to differences in polarity.[4] Digoxin is a polar compound, although not nearly as polar as ouabain and deslanoside, whereas digitoxin is a nonpolar compound. Polar compounds are less lipid soluble and, therefore, less well absorbed, less completely bound to serum albumin (leading to a lower serum concentration), and have less renal tubular reabsorption. This results in predominant urinary elimination of the drug and thus a shorter half-life. However, this also

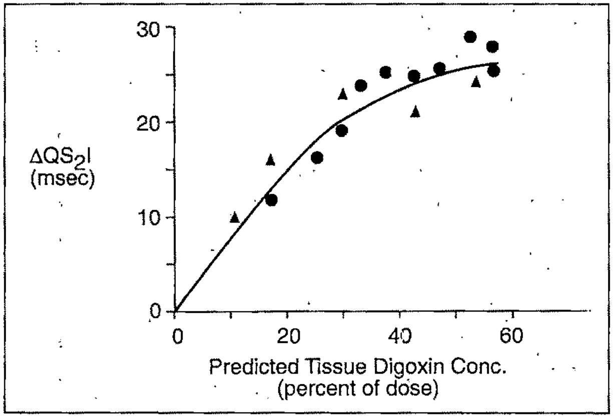


FIGURE 6. Correlation of the change in the duration of electromechanical systole corrected for heart rate (ΔQS_2I) and predicted tissue digoxin concentrations derived from serial measurements of plasma digoxin concentrations after administration of 1 mg digoxin intravenously in 10 normal subjects: 22 QS_2I and plasma digoxin concentrations were measured simultaneously over a 96-hour period. *Circles* represent points from onset to peak activity; *triangles* represent the decay portion. The nonlinear correlation was r = 0.97 ($p < 0.01$). (Reprinted with permission from *J Pharmacokinet Biopharm*.[12])

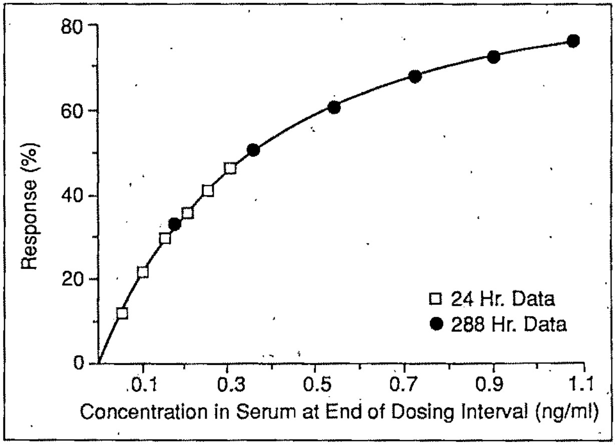
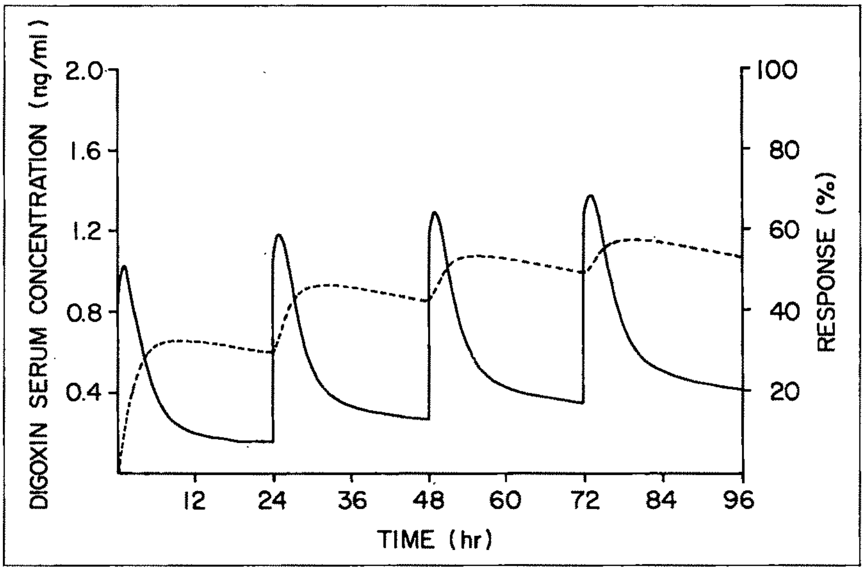


FIGURE 7. Nonlinear relation between response (percent of maximum) and serum digoxin concentration at 24 hours postdose. Data were obtained from simulations using either single oral doses (0.125–0.75 mg, □) or multiple oral doses (0.125–0.75 mg, ●) every 24 hours for 12 days. The relation does not depend on the number of doses given and applies only to the postabsorption, postdistributive phase of the serum concentration-time curve (about 12–24 hours postdose). (Reprinted with permission from *J Clin Pharmacol*.[14])

FIGURE 8. Simulated time profile of serum digoxin concentrations (*solid line*) and tissue response as judged by the duration of electromechanical systole corrected for heart rate (QS_2I) (*dashed line*) over a 4-day period. The tissue response is plotted as a percentage of maximum response. Pharmacokinetic and pharmacodynamic constants for the simulation were obtained from a single-dose study in normal humans. The dosage regimen for the simulation was 0.375 mg/day digoxin tablets with a bioavailability of 0.8. (Reprinted with permission from *Applied Pharmacokinetics*.[15])



leads to variability in elimination because of the many factors that can affect renal function (reviewed later). The basic pharmacokinetic parameters of digoxin are listed in Table II.

In the early 1970s, the poor bioavailability of several digoxin formulations (*not* including Lanoxin) was documented, which led to strict Food and Drug Administration guidelines for digoxin manufacturers to ensure adequate bioavailability.[16] More recently, Lanoxicaps have been developed. This digoxin formulation has improved oral bioavailability.[17]

Substances that can affect digoxin bioavailability are listed in Table III. Cathartics and antacids inhibit digoxin absorption, as does diarrhea.[18,19] Cholesterol-binding agents bind digoxin in the gut and inhibit absorption.[20] Digoxin malabsorption can occur with most small bowel disorders, including the edematous bowel of patients with chronic CHF.[21,22] In all of these settings the Lanoxicap formulation of digoxin is more bioavailable and is, therefore, recommended.[15]

Up to 10% of the population in the United States carries the intestinal bacterium *Eubacterium lentum*, which hydrolyzes digoxin to the inactive metabolite dihydrodigoxin.[23] Curiously, this bacterium is far more common in urban dwellers.[24] Antibiotic therapy in these patients may abruptly increase the serum digoxin concentration.[25] Omeprazole increases bioavailability by inhibiting the breakdown of digoxin by gastric acid.[26]

The distribution of digoxin is affected by a number of physiologic and pathophysiologic factors.[4,24,27,28] Binding of digoxin to the sodium–potassium adenosine triphosphatase (Na^+,K^+-ATPase) receptor is directly related to serum potassium concentrations: it is enhanced in patients with hypokalemia and inhibited in those with hyperkalemia. Since this binding is reversible, potassium administration may cause unbinding.

Fifty percent of digoxin in the body is bound to the Na^+,K^+-ATPase receptor in skeletal muscle.[29,30] Physical activity increases binding and can produce a substantial lowering of the serum digoxin concentration (by up to 33%). Older individuals have relatively fewer binding sites for digoxin. Pregnancy and hyperthyroidism each increase the

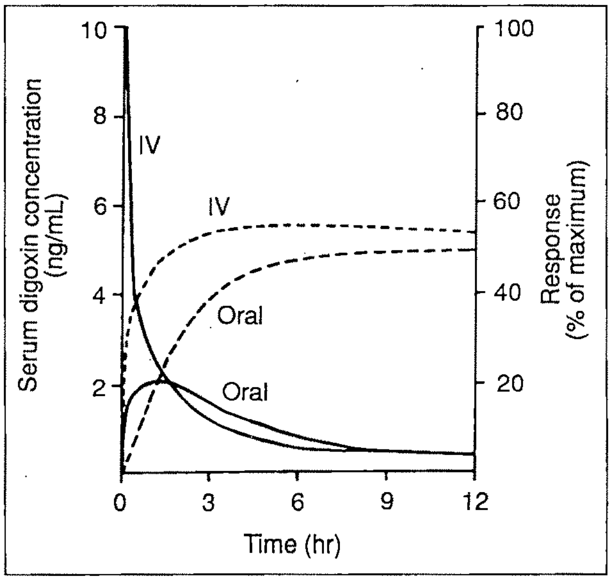


FIGURE 9. Plot of simulated serum digoxin concentration (*solid lines*) and response intensity (*dashed lines*) as a function of time comparing a single oral dose (0.75 mg) and an intravenous dose of equivalent bioavailability (0.6 mg). (Reprinted with permission from *J Clin Pharmacol*.[14])

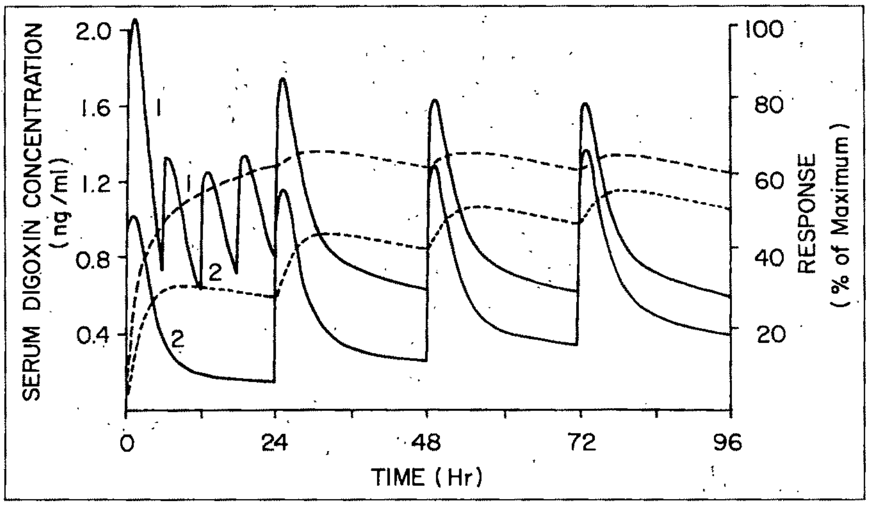


FIGURE 10. Plot of simulated serum digoxin concentration (*solid lines*) and response intensity (*dashed lines*) as a function of time comparing protocols with and without an oral loading dose in normal subjects. Regimen 1: 0.75 mg at 0 hours, 0.25 mg at 6, 12, and 18 hours, and 0.375 mg at 24, 48, and 72 hours; regimen 2: 0.375 mg at 0, 24, 48, and 72 hours. (Reprinted with permission from *J Clin Pharmacol*.[14])

number of digoxin binding sites, whereas hypothyroidism decreases the number. Digoxin is not bound by adipose tissue, so the dose should be based on lean body mass.[31] Amiodarone may affect digoxin's volume of distribution and therefore increase the serum concentration.[32] Renal failure produces an increased serum digoxin concentration; it is unclear whether this represents a diminished volume of distribution for digoxin or an accumulation of hepatic digoxin metabolites.[15]

Digoxin elimination is predominantly renal, although newer evidence indicates hepatic metabolism is more extensive than was previously believed.[15,26] When renal function is reduced (e.g., via intrinsic renal disease, aging, excessive diuretics, or severe heart failure), there is more extensive hepatic metabolism and fecal excretion. Impaired renal elimination of digoxin can be induced by indomethacin, cyclosporine, or spironolactone, apparently by their direct effects on the kidney.[33,34] Quinidine inhibits renal excretion of digoxin.[35,36] Other antiarrhythmic agents also increase serum digoxin concentrations, but the mechanisms are not exclusively renal.[37–40] Vasodilators, by increasing renal blood flow, can enhance renal excretion. Since the increased serum digoxin concentrations reflect biologically active compounds in these settings, the dose should be reduced, generally by half.[41,42] Obviously, measurement of serum digoxin concentrations is critical to its safe and proper use.

DIGOXIN DOSING

In the early 1970s, population-based nomograms were advocated for digoxin dosing.[43] Because of marked individual variability, however, these nomograms did not achieve widespread acceptance. An alternative approach has been to select an empiric dose based on parameters like body mass, renal function, and drug interactions, and subsequently monitor serum digoxin concentrations. The goal is to achieve a desired body pool of 10 μg/kg or a serum digoxin concentration of approximately 1.5 ng/mL.[4,15] A 75% absorption of tablets or 90% absorption of Lanoxicaps is as-

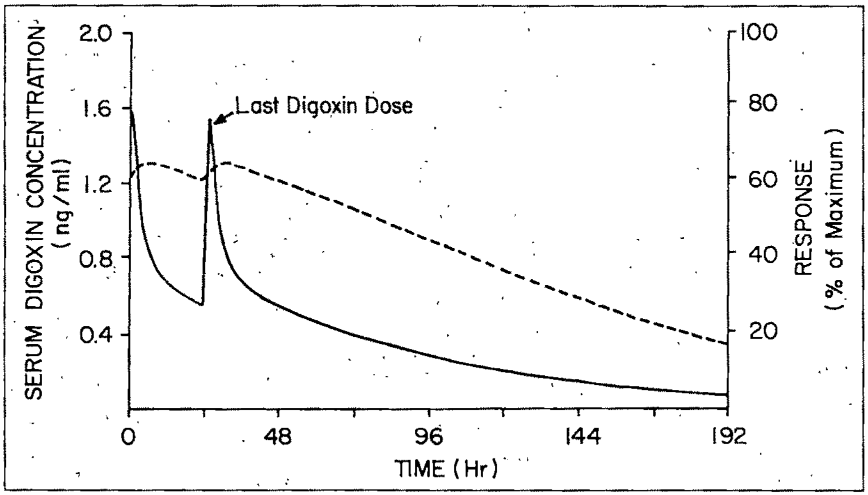


FIGURE 11. Simulation of the effect of interrupting a multiple-dose digoxin regimen by omission of several doses. An oral regimen of 0.375 mg/day was given until steady state was attained and then stopped. Only results from the last 2 doses are shown. Simulations are for serum digoxin concentration (*solid line*) and response (*dashed line*) as a function of time. (Reprinted with permission from *J Clin Pharmacol*.[14])

sumed. A baseline serum digoxin concentration should be obtained to determine the presence of digitalis-like immunoreactive substances, as will be discussed later.

In many instances, a loading dose of digoxin is not required.[44] A maintenance dose of 0.25 mg is started when creatinine clearance exceeds 20 mL/min; when creatinine clearance is less than 20 mL/min, the maintenance dose is 0.125 mg. The serum digoxin concentration is measured 2 days later. This point generally represents 50% of the eventual steady-state concentration. If an exceedingly high or exceedingly low serum digoxin concentration is present, the maintenance dose can be adjusted accordingly. A repeat concentration is then obtained 5 half-lives after a dosing change.

If a loading dose is preferred, the serum digoxin concentration should be measured 12 hours after the last loading dose. This will indicate whether the desired body pool has been achieved. The maintenance dose is then based on predicted half-life, and the serum digoxin concentration is remeasured in 2 days, as discussed above.

DIGOXIN ASSAYS

Most clinically used digoxin assays are RIAs.[28,45] These are sensitive to levels of 0.2–0.4 ng/mL and have a coefficient of variance of 5–15%. Errors are related to differences in assay kits as well as laboratory technique. It is, therefore, essential for the clinician to know the reproducibility of serum digoxin concentrations in the laboratory.

Unfortunately, the RIA has relatively low specificity and cross-reacts with digitalis-like immunoreactive substances, which may be present in renal failure, hepatic failure, pregnancy, some hypertensive states, and CHF.[4,15,28,46,47] Whether these substances are truly digitalis is still unclear, but they can comprise up to 50% of the serum digoxin measured by RIA. Fortunately, most active digoxin metabolites, including digoxigenin and bisdigoxiside and monodigoxiside, react with most assays. Dihydrodigoxin, which is inactive, does not cross-react with most assays, but is usually present at low concentrations in the serum.

Other assay methods include the enzymatic immunoassay and fluorescent polarization immunoassay. These have sensitivities and specificities similar to those of the RIA. The most specific assay for digoxin is that obtained with high-performance liquid chromatography. This method is tedious, however, and not currently available for clinical use.[48] A promising new approach is to use digoxin-specific monoclonal antibodies.[49]

TABLE II Digoxin Pharmacokinetic Parameters

Total body clearance	180 mL/min/m²
Renal clearance	140 mL/min/m²
Bioavailability	
Tablets	60–75%
Elixir	75–85%
Lanoxicaps	80–90%
Percent excreted in urine as native drug	
Intravenous dose	72%
Oral dose	54%
Half-life	
Serum	36 hours
Tissue	44 hours

INDICATIONS FOR SERUM DIGOXIN LEVELS

Table IV lists the indications for the serum digoxin RIA. These include validating the dose, assessing patient compliance, evaluating bioavailability, and assessing the effects of renal function or of other drugs on elimination.[50] The assay also may be used when there has been a hemodynamic or clinical change (e.g., worsening heart failure,

TABLE III Digoxin Pharmacokinetic Interactions

- **Bioavailability**
  - *Decreased*
    - Cathartics
    - Antacids
    - Cholesterol-binding agents
    - Malabsorption syndromes
    - Bowel edema
    - *Eubacterium lentum*
    - Gastric hyperacidity
  - *Increased*
    - Lanoxicaps or elixir
    - Antibiotics (*E. lentum*)
    - Omeprazole
- **Distribution**
  - *Decreased*
    - Renal failure
    - Hyperkalemia
    - Aging
    - Hypothyroidism
    - Amiodarone
  - *Increased*
    - Hypokalemia
    - Hyperthyroidism
    - Pregnancy
    - Physical activity
- **Elimination**
  - *Decreased*
    - Renal failure
    - Excessive diuretics
    - Aging
    - Indomethacin
    - Cyclosporine
    - Spironolactone
    - Verapamil
    - Quinidine
    - Propafenone
  - *Increased*
    - Diarrhea
    - Vasodilators

TABLE IV Indications for Serum Radioimmunoassay of Digoxin

Validate dose
Assess compliance
Assess bioavailability
Assess effect of renal function on elimination
Assess effect of other pharmacologic agents on elimination
Assess effect of hemodynamic change
Assess patients who fail to respond
Prevent toxicity
Diagnose toxicity

acute myocardial infarction), apparent failure to respond to digoxin, or in the diagnosis and prevention of digoxin toxicity. Once steady state has been reached, measurement more than annually is seldom required.

Computer-assisted surveillance of digoxin dosing has been advocated to reduce toxicity and improve efficacy.[51–55] Although this approach appears to have merit, it remains a "hypothesis in need of testing."[56]

A major error in the use of serum digoxin assays is the failure to wait for equilibration, which requires 12 hours following an oral dose. In our institution, digoxin is administered in the evening so that the morning blood sample is taken 12 hours later. Because there can be a substantial difference between the serum digoxin concentration at 8 hours and at 24 hours postdose, a standard collection time should be specified and implemented. In outpatients there should be at least a 1-hour rest period prior to obtaining the sample, since physical activity can reduce the blood level.[57] When ordering a digoxin assay, the clinician must always consider whether a steady state has been reached, and remember that this takes 5 half-lives (range, 10–20 days) following any change in the dose.

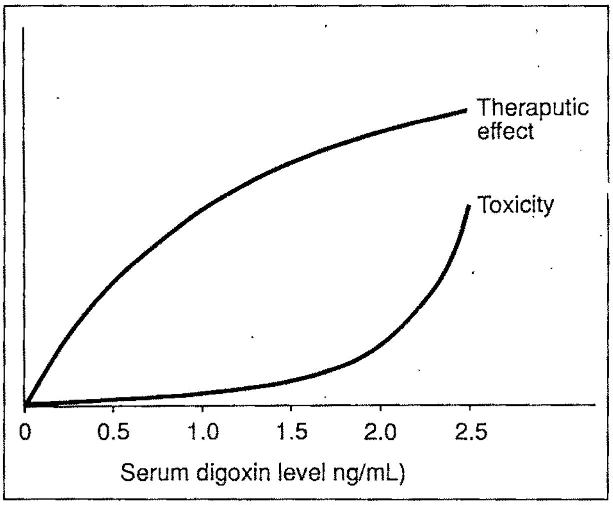


FIGURE 12. Schematic illustration of the relation between the therapeutic effect of digoxin, the toxic effect, and the serum digoxin concentration. Above a serum digoxin level of 2.0 ng/mL, there is minimal further therapeutic effect but a dramatic increase in the toxic effect. (Reprinted with permission from *Cardiotonic Drugs*.[4])

The digoxin assay is one of the most widely used drug assays and represents a considerable medical care cost.[58] Unfortunately, a significant percentage of digoxin assays are not necessary and generally reflect a poor understanding of digoxin pharmacokinetics. This is clearly an area where education (and perhaps computer surveillance) could produce both cost savings and improved digoxin usage.

Finally, there is the question of the role of the serum digoxin concentration to assess the clinical response to digoxin. Traditional clinical parameters (slowing of heart rate, initiation of diuresis, improvement in dyspnea, disappearance of an S_3 gallop, improvement in chest radiograph, etc.) used to assess response to digoxin continue to be most important. When atrial fibrillation is present, the ventricular rate is used as a therapeutic end point. As noted elsewhere in this symposium, however, the usual therapeutic concentration of digoxin may not always be sufficient to slow ventricular rate, especially in acutely ill patients. In such cases, adding another agent is generally preferred over increasing the serum digoxin concentration to the toxic range.

When a patient in sinus rhythm has had a suboptimal clinical response to chronic digoxin administration, the serum concentration is uniquely important for determining whether the dose should be increased. Several studies [59–62] have suggested that patients with steady-state serum digoxin concentrations <1 ng/mL show subjective and objective improvement when the serum concentration is raised closer to 1.5 ng/mL. Because of the current practice to initiate therapy with 0.25 mg (rather than 0.375 mg) digoxin in all cases, a significant number of heart failure patients have sustained subtherapeutic serum digoxin concentrations.

Figure 12 schematically illustrates the relation between serum digoxin concentration, physiologic effect, and toxicity.[4] It is based on empiric observations of digitalis toxicity and the dose-response curve of digoxin. If a steady-state therapeutic concentration between 1.0 and 1.5 ng/mL is achieved, then near-maximal digoxin effect will be achieved with a low risk of toxicity.

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DISCUSSION

Dr. Leier: What are your thoughts about endogenous digitalis-like substances? I doubt if these are measurable with the techniques you talked about.

Dr. Lewis: They are measurable by the radioimmunoassay. Actually, they have been measured in concentrations of 3–5 ng/mL in neonates. Interestingly, they seem to appear in volume-overload states. Some investigators think that digitalis is a primitive hormone, just as opiates are primitive hormones. Like opium, it is found in plants, but whether the substance we are measuring is a primitive hormone is just not clear.

Dr. Leier: Why do we have digoxin receptors? Do you think it is because of this endogenous digitalis-like substance, or is it another receptor that digoxin happens to borrow?

Dr. Lewis: I do not know. I think digitalis may be a primitive hormone.

Dr. Kelly: It is a misnomer to say it is a receptor. There is a binding site in one of the subunits that binds cardiac glycosides, but I do not think it is any different from any other highly conserved orientation of a membrane ion-transporting protein. It is not a receptor, it is not hooked to a guanine protein (G protein). It is not at all like opiate receptors, for example. It is more like calcium channels, to which are bound dihydropyridines that affect cardiac function.

Digoxin binds to one conformation of the sodium pump and affects the pumping cycle, but it is not like a receptor. Why that conformation has been so highly conserved is the question. That is why people continue to look for endogenous digoxin. An article by Hamlyn and colleagues,[1] a reputable group, reports that they have looked at it for many years and believe it is ouabain. Others of us believe that this is just not the case.

Dr. McCall: They are the second group to demonstrate, by high-performance liquid chromatography and by chemical analysis, that it is ouabain. It had been described by another group previously.

Dr. Kelly: There is disagreement, anyway.

Dr. Gheorghiade: In practice, most physicians will not measure serum digoxin concentrations to maximize the dose. Interestingly, approximately 14,000 serum digoxin concentrations were measured at our institution over a 2-year period, and in many were <0.9 ng/mL.[2]

Dr. Lewis: It is the same at our institution.

Dr. Gheorghiade: The question then is, are we really optimizing therapy? For example, in the Digoxin–Captopril study, the mean serum digoxin concentration was approximately 0.9 ng/mL.

Dr. Lewis: When I was a medical student, I was given a handout that listed digitalizing doses; the doses on that are twice what we use today. The digitalizing dose of digoxin was 3 mg; the maintenance dose was 0.5 mg. Today, everybody gets 0.25 mg whether they are 280 lb or not. It is amazing. People do not realize that the dose should be based on body size, and the average dose should be 0.375 mg.

Dr. Gheorghiade: You are right. It is difficult to assess efficacy of a drug if the right dose is not being used.

Dr. Yusuf: But what is the right dose?

Dr. Gheorghiade: In a recently completed study we have seen a significant increase in rest and exercise ejection fraction in patients with CHF when the serum concentration of digoxin was increased from 0.7 to 1.2 ng/mL.

Dr. Yusuf: What is the basis for that statement? I can understand using that dose range in patients with atrial fibrillation, but what is the clinical basis for using it, say, in cases of heart failure in sinus rhythm?

Dr. Gheorghiade: In a study by Johnston and McDevitt[3] in which patients with CHF were evaluated following withdrawal of digoxin therapy, only 1 of the 34 patients with a serum level <0.8 ng/mL deteriorated when digoxin was discontinued. In contrast, 7 of 22 patients with a serum level that was considered therapeutic (0.8–2.0 ng/mL) deteriorated when digoxin was withdrawn. However, I agree with you that there are no good studies to suggest that the digoxin dose for "optimal" clinical and hemodynamic effects is one that provides a serum concentration of 1–2 ng/mL.

Dr. Yusuf: Response is not a yes-or-no phenomenon. So there is probably a substantial degree of response, even in patients receiving a dose that gives a serum digoxin concentration of 0.8 ng/mL. There is also very good anecdotal evidence—and it s unusual for me to call anecdotal evidence very good—that digoxin toxicity is relatively rare compared with 3 decades ago. This may be explained partially by the fact that we have been using lower doses.[4]

Dr. Leier: Anecdotally, I do not remember ever improving a patient's cardiac function by doubling the dose or by increasing the serum digoxin concentration from 0.7 to 1.4 ng/mL, unless the patient had atrial fibrillation.

Dr. Lewis: A number of heart failure patients report to us with serum digoxin concentration <0.4 ng/mL. I do not know whether that is because they are not taking it or because they are not absorbing it due to bowel edema. Personally, I try to keep the serum digoxin concentration around 1.2 ng/mL.

Dr. McCall: Maybe the old physicians were right: initiate therapy with toxic levels of digoxin and then taper the dose.

Dr. Leier: I would go by the other philosophy, that is, a little bit of digoxin is better than no digoxin, and it is better than too much digoxin.

Dr. McCall: What we are talking about is where do you get the maximum effect, whatever that is, for the individual patient?

Dr. Gheorghiade: Now that we know more about drug interactions and serum concentrations, maybe it would be reasonable and safer to increase the dose in patients who continue to have symptoms and signs of heart failure and the serum digoxin concentration is <0.9 ng/mL.

Dr. Lewis: I think that is one of the reasons many people have stated digoxin is a mild inotrope. Just parenthetically, the maximum effect you get with digoxin on systolic intervals is about the equivalent of 2 μg/kg isoproterenol. So, intravenous digoxin is not a mild inotropic drug.

Dr. Gheorghiade: Ware et al[5] examined 20 older patients, mean age 83.8 years. They reported that ejection fraction increased with digoxin and the maximum improvement in ejection fraction occurred at the level of 1.0 ng/mL.

Dr. Lewis: And very rarely produced toxicity.

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Recognition and Management of Digitalis Toxicity

Ralph A. Kelly, MD, and Thomas W. Smith, MD

The most important step in the management of toxicity due to any of the cardiac glycosides is its recognition. Despite the development of an accurate clinical assay for serum levels of digoxin >20 years ago, digitalis toxicity remains common and difficult to confirm, even if suspected, due primarily to 2 factors. First, the signs and symptoms of digitalis toxicity, most commonly an abnormal electrocardiogram showing ventricular or atrial arrhythmias, with or without some degree of concurrent atrioventricular block, often also occur in patients with congestive heart failure (CHF) and underlying coronary atherosclerosis who are not receiving a cardiac glycoside. Second, due to digoxin's narrow therapeutic ratio, the marked degree of variability in the sensitivity of individual patients to its toxic effects, and the common problem of obtaining blood samples inappropriately during the early distribution phase following dosing, a serum digoxin concentration often does not serve as a reliable indicator of toxicity. Despite these difficulties in diagnosis, the management of digoxin toxicity has been made much more effective with the widespread availability of F(ab) fragments of antidigoxin antibodies. This drug provides the clinician with a rapidly acting, safe antidote for all commonly used digitalis preparations. Conventional therapy for digoxin toxicity remains the maintenance of serum potassium levels ≥4 mEq/liter, reversal of decompensated CHF or overt myocardial ischemia, attention to serum magnesium levels and the patient's acid–base status, appropriate antiarrhythmics in the event of ventricular arrhythmias, and a temporary pacemaker for high-grade atrioventricular block. Nevertheless, the high specificity and documented safety of the antibody preparation provides a needed safety net for the continuing use of cardiac glycosides as first-line inotropic agents in the modern therapy of chronic CHF.

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With the advent in the past two decades of new classes of drugs for the treatment of congestive heart failure (CHF) and supraventricular arrhythmias, as well as results from well-designed prospective clinical trials that have more clearly defined the role of cardiac glycosides in CHF, the incidence of digitalis toxicity in patients with CHF has declined. In addition, a new therapeutic modality specific for digitalis intoxication—the use of F(ab) fragments of antidigoxin antibodies—has proven to be safe and effective in the treatment of life-threatening digoxin toxicity.

INCIDENCE OF DIGITALIS INTOXICATION AND MORTALITY

Although cardiac glycoside toxicity can be suspected based on nonspecific symptoms and electrocardiographic findings, it is often difficult to document. It is particularly difficult to evaluate epidemiologic data from studies on the incidence of digoxin toxicity that were performed before the development of assays to measure serum digoxin concentrations. Nevertheless, studies published in the 1960s and early 1970s found that approximately 20% of patients receiving maintenance digoxin therapy demonstrated signs or symptoms of toxicity at some point in their clinical course.[1,2] In a prospective clinical trial, Beller et al[3] reported that 17% of patients receiving maintenance digoxin or digitoxin therapy who required hospitalization showed definite evidence of toxicity, and another 4% had probable toxicity. These results are similar to the estimate of overt digoxin or digitoxin toxicity in hospitalized patients in the Boston Collaborative Drug Surveillance Program, which reported an incidence of 13% in 1972.[4] The marked variability

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TABLE I Laboratory Data and Mortality in 219 Patients With Discharge Diagnosis of Digoxin Intoxication

Diagnosis	Patients (n)	Digoxin Level (ng/mL)	Serum BUN (mg/dL)	Serum Creatinine (mg/dL)	Serum Potassium (mEq/liter)	Deaths[†] (n)
Definite	43	4.1 ± 2*	42 ± 21*	2.5 ± 2*	4.7 ± 1*	2
Possible	133	3.4 ± 1	41 ± 33	2.4 ± 2	4.6 ± 1	9
Nontoxic	43	1.7 ± 1*	28 ± 20*	1.6 ± 1*	4.1 ± 1*	0

*$p < 0.05$ between definitely toxic vs nontoxic groups.
[†]Nine of 11 deaths resulted from causes other than digoxin intoxication.
BUN = blood urea nitrogen.
Adapted with permission from *Am Heart J*.[9]

in digoxin bioavailability from manufacturer to manufacturer also resulted in episodes of increased toxicity due to a hospital's change in formulation or vendor; one medical ward, for example, reported 15 concurrent cases of digitalis toxicity in a 30-bed unit.[5]

The introduction in 1969 of a sensitive radioimmunoassay for serum digoxin concentrations, and its widespread acceptance and availability, has made this technique useful in the assessment of suspected digitalis toxicity.[6,7] Nevertheless, considerable overlap of serum concentrations exists between populations of patients with and without clinical signs and symptoms of digoxin toxicity. Also, there is only a poor correlation between the ventricular response rate at rest and serum digoxin concentrations in patients with atrial fibrillation who are taking digoxin. Other tests have been proposed to aid in the diagnosis of digitalis toxicity, such as a patient's response to the ultra-short-acting cardiac glycoside acetyl-strophanthidin,[8] but this approach is regarded as too dangerous for routine clinical use.

Nevertheless, the general impression is that the incidence of digitalis toxicity has fallen since the availability of the digoxin assays. This is due in part to the development of newer classes of drugs for the treatment of both supraventricular arrhythmias and CHF, and to the recognition of important drug interactions between digoxin and other commonly used cardiovascular agents, such as quinidine. A large prospective epidemiologic study by Mahdyoon et al,[9] who examined 994 patients admitted to a large urban teaching hospital with the diagnosis of CHF, supports this. Of this group, 56% were receiving maintenance digoxin, but only 4 patients (0.8%) were classified as definitely being digoxin toxic, and another 16 (4.0%) were classified as possibly digoxin toxic. The diagnosis of digitalis toxicity was based on the presence of both symptoms and electrocardiographic signs consistent with digoxin toxicity, a serum digoxin concentration of at least 1 ng/mL, and, importantly, a close time correlation between resolution of evidence of toxicity and drug withdrawal or administration of antidigoxin F(ab) fragments.[9]

Mahdyoon et al[9] also retrospectively analyzed mortality due to digoxin intoxication in 219 patients discharged from the hospital over an 8-year period with the diagnosis of digitalis toxicity while receiving maintenance digoxin therapy (i.e., excluding those patients who had accidentally or with suicidal intent consumed large quantities of digoxin). Earlier studies of mortality in patients diagnosed with digoxin intoxication are difficult to evaluate due to the absence of serum level data in most cases, or to reliance on criteria that were too nonspecific to allow a conclusive diagnosis of toxicity. In the study reported by Beller et al,[3] the mortality rate was 41% in patients with "definite" intoxication (although only rarely due to digitalis toxicity per se) and only 17% in digitalized patients not showing signs or symptoms of digoxin toxicity. In marked contrast, Mahdyoon et al[9] demonstrated a mortality rate of 4.6% in patients with documented digoxin toxicity, as classified by their rather rigorous criteria. As shown in Table I, of the 11 deaths in the 2 groups of patients originally classified as "digoxin toxic" prior to retrospective analysis of their medical records, only 2 patients were thought to have definitely died of digoxin toxicity.[9] Thus, the true mortality rate was probably $<1\%$. This is consistent with the low mortality rate for digoxin toxicity reported in the Boston Collaborative Drug Surveillance Program.[4] Other serious manifestations of digoxin toxicity in the retrospective trial by Mahdyoon et al[9] were also uncommon and treated effectively with standard therapy. Although 33% of the definitely toxic patients demonstrated second- or third-degree atrioventricular (AV) block, only 5% required a temporary pacemaker.

Reasons for the low incidence of digoxin toxicity and the low morbidity and mortality rates observed in the recent trial by Mahdyoon et al,[9] compared with older studies, are changes in patients' characteristics and in the management of patients given

TABLE II Factors Associated With Increased Risk for Digitalis Intoxication

Renal insufficiency
Type and severity of underlying cardiac disease
Electrolyte abnormalities (especially $\downarrow K^-$, $\downarrow Mg^{2+}$, $\uparrow Ca^{2+}$ serum levels)
Hypothyroidism
Advanced pulmonary disease
Pharmacokinetic interactions with other drugs (especially quinidine, verapamil, and amiodarone)
Pharmacodynamic interactions (especially with sympathomimetic and sympatholytic agents)

long-term digitalis therapy. In the 1971 prospective trial by Beller et al,[3] >70% of the patients had coronary artery disease and 60% had had a previous myocardial infarction; in the 1990 study by Mahdyoon et al,[9] these numbers were 35% and 20%, respectively. In past studies, hypokalemia had often been implicated as a major complicating factor contributing to serious morbidity in patients receiving long-term digoxin therapy. In a 1978 study by Lehmann et al,[10] the incidence of digitalis toxicity was 13% in >4,600 cardiology admissions and was considered life-threatening in nearly half. Most of the more serious arrhythmias—ventricular tachycardia, ventricular fibrillation, accelerated junctional rhythms, and advanced AV nodal block—were found in hypokalemic patients (i.e., potassium <3.7 mEq/liter).[10] Shapiro[11] noted that in patients with arrhythmias consistent with digoxin intoxication, serum digoxin concentrations were 3 times higher in hypokalemic versus normokalemic patients. In contrast, as shown in Table I, patients in the recent study by Mahdyoon et al[9] were generally normokalemic, older, and had moderate renal insufficiency. Finally, although variations in bioavailability among formulations and absence of serum levels in older studies make comparison with contemporary clinical practice difficult, the standard loading and maintenance doses of digitalis preparations used today appear to be lower.[12–14] This is supported by the higher prevalence of supraventricular arrhythmias, with or without AV block, and more severe ventricular arrhythmias, often associated with higher serum digitalis concentrations, reported in the older studies.[15]

Despite the more benign character of digoxin intoxication in recent years, the role of cardiac glycosides in contributing to excess cardiovascular mortality following myocardial infarction remains controversial. Two retrospective analyses of cardiac glycoside use in postmyocardial infarction patients reported in the early 1980s found that digoxin increased mortality,[16,17] even when allowances were made for the fact that those patients given digoxin were generally more ill. However, several other large clinical trials reported in the last decade have failed to confirm this, after all relevant and identifiable factors that could also have independently contributed to mortality were taken into account.[18–21] The evidence now suggests that digoxin does not demonstrably increase mortality following myocardial infarction, although there is also no evidence that digoxin improves survival in this (or any other) group of patients. With enrollment into a large, prospective, randomized, double-blind trial sponsored by the National Institutes of Health, the Digoxin Investigator Group Trial, now well under way, it should be possible to determine by the mid-1990s whether digoxin improves survival. This study should also resolve whether digoxin improves symptoms in patients with chronic CHF.

CARDIAC MANIFESTATIONS OF DIGOXIN TOXICITY

Although the incidence of serious digitalis toxicity and associated mortality may have declined over the past several decades, recent studies on efficacy, discussed elsewhere in this symposium, suggest that digoxin is most effective in patients with moderate to severe left ventricular dysfunction, many of whom also have underlying ischemic disease. Such patients are at greater risk for digitalis toxicity, due to their underlying cardiac disease and the increased prevalence of concurrent acid–base and electrolyte disturbances (Table II).

Although there are no arrhythmias diagnostic of digoxin toxicity, toxicity should be suspected in any patient receiving the medication who exhibits evidence of both increasd automaticity and depressed conduction. Rare arrhythmias such as fascicular tachycardia, ventricular bigeminy with alternating right- and left-axis deviation and bidirectional ventricular tachycardia are highly suggestive of digoxin toxicity, as is the development of repetitive and multiform ventricular premature beats during atrial fibrillation in a patient whose ventricular response rate had been well controlled previously with digoxin. Even with a serum digoxin concentration of >2 ng/mL, the wide overlap between patients with and without toxicity limits the ability of the serum digoxin concentration to confirm (or deny) toxicity's existence. Only a temporal correlation with drug withdrawal, or a prompt termination of the arrhythmia after administration of F(ab) fragment of antidigoxin antibodies, is confirmatory.

Atrium and atrioventricular node: In patients in sinus rhythm, cardiac glycosides often slow the heart rate, usually as a result of decreased adrenergic tone. This is due partly to enhanced cardiac performance and partly to a direct drug effect to increase baroreceptor responsiveness. Toxic digoxin concentrations may lead to sinus arrest or sinus exit block, however, due to a direct drug effect on the sinoatrial node.[22] Although atrial tissue is not affected by therapeutic digoxin concentrations, higher serum levels may lead to increased automaticity and a decline in conduction velocity. The effect of cardiac glycosides in slowing AV nodal conduction and prolonging nodal refractoriness is largely mediated by enhanced parasympathetic and decreased adrenergic tone. At toxic levels, however, digoxin appears to act directly to prolong the AV nodal refractory period. This effect, along with increased vagal tone, may lead to advanced AV junctional conduction block. Also, junctional pacemakers may begin to discharge at increasing frequency, resulting in a nonparoxysmal, automatic AV junctional tachycardia. This is often recognized clinically as a paradoxic regularization of ventricular rate in chronic atrial fibrillation. Other supraventricular arrhythmias include AV nodal reentrant tachycardias and tachycardias that originate from enhanced atrial automaticity. Although paroxysmal atrial tachycardia with block ("PAT with block") is associated with digitalis toxicity, there are no features of this arrhythmia that clearly distinguish whether it is due to digitalis intoxication.[23]

AV junctional block of varying degrees, along with increased ventricular automaticity, are the most common manifestations of digoxin toxicity, occurring in 30–40% of patients with recognized digoxin toxicity.[9,24] Although first-degree AV block is often a simple indication of digitalis effect, higher degrees of AV block are evidence of digoxin toxicity. Second-degree AV block typically has a Wenckebach periodicity, whether or not the patient is in sinus rhythm or automatic atrial tachycardia. Mobitz type II second-degree AV block due to digoxin intoxication alone is rare. Third-degree AV block should be distinguished electrocardiographically from apparent AV dissociation due to an accelerated idioventricular or AV junctional pacemaker.

Purkinje fibers and ventricular muscle: The toxic manifestations of cardiac glycosides in ventricular tissue are primarily due to enhanced automaticity and triggered activity. Ventricular arrhythmias are uncommon, however, in young patients with healthy hearts even after suicidal ingestion of a large quantity of digoxin. This suggests that in older patients with underlying heart disease, enhanced Purkinje fiber automaticity in digitalis toxicity may be exacerbated by ischemia, fiber stretch, or other injury. The degree of diastolic depolarization observed with cardiac glycoside intoxication also increases with ventricular rate and drug level. A second contributing mechanism includes spontaneous depolarizations triggered by previous action potentials, or "delayed after-depolarizations." These may be related to a transient decrease in membrane potential late in phase 3 or early in phase 4 that reaches threshold and depolarizes the ventricle. The likelihood that an after-depolarization will reach threshold is enhanced by hypokalemia or hypercalcemia and may be induced by catecholamines and digitalis glycosides in isolated Purkinje fibers. Although triggered activity is a plausible explanation for many digitalis-induced ventricular arrhythmias, it has not been proven in humans.[25]

The most common manifestation of digitalis toxicity is an increase in the frequency of ventricular premature beats of any morphology, with either fixed or varying coupling intervals to preceding supraventricular beats. As noted, bidirectional and fascicular tachycardias may occur and are very suggestive of digitalis toxicity. Ventricular fibrillation is rarely the first electrophysiologic manifestation of digitalis toxicity. Again, although there is no one electrocardiographic abnormality that is pathognomonic of digoxin toxicity, the combination of enhanced automaticity and impaired conduction (e.g., AV block accompanied by an accelerated junctional pacemaker) is highly suggestive of toxicity even in patients with serum levels of 1–2 ng/mL.

EXTRACARDIAC MANIFESTATIONS

The noncardiac manifestations of digitalis toxicity are nonspecific but highly prevalent in patients with known or suspected digoxin toxicity (Table III). Most patients experience fatigue and often anorexia is an early complaint, followed by nausea and occasionally vomiting due to central effects of these drugs. A somewhat more specific, if uncommon, complaint is visual symptoms, particularly halos around bright objects and changes in color perception, in addition to more common neurologic manifestations such as headache, neuralgic pain, and confusion.

TABLE III Frequency of Symptoms Associated With Digoxin Intoxication

	Definite (%)	Possible (%)	Nontoxic (%)
Nausea	52	30	27
Vomiting	48	30	27
Anorexia	34	27	18
Dizziness	14	19	23
Fatigue	14	16	11
Visual disturbances	9	5	7
Syncope	6	3	2
Abdominal pain	6	4	0
Diarrhea	2	2	2
Headache	0	2	0
Delirium	0	1	0

Reprinted with permission from *Am Heart J*.[9]

TABLE IV Acute Potassium Administration in Suspected Digitalis Toxicity

Indications
Serum potassium <4.0 mEq/liter
  VPCs; VT
  SVT with AV block
Serum potassium <3.0 mEq/liter (in addition to those listed above)
  First-degree AV block and second-degree AV block with Wenckebach periodicity (Mobitz I)

Contraindications
Mobitz type II or third-degree AV block if temporary electrical pacing unavailable

AV = atrioventricular; SVT = supraventricular tachycardia; VPCs = ventricular premature complexes; VT = ventricular tachycardia.

FACTORS CONTRIBUTING TO INCREASED RISK OF DIGOXIN TOXICITY

Electrolyte abnormalities: Changes in potassium homeostasis clearly influence the action of digitalis. Cardiac glycoside binding to sarcolemmal sodium–potassium adenosine triphosphatase, (Na^+,K^+-ATPase), the "sodium pump," is affected by the plasma potassium concentration.[26] This is, at least in part, because the association of potassium with Na^+,K^+-ATPase results in dephosphorylation of the enzyme, including a conformational change that reduces the likelihood that a cardiac glycoside will successfully bind to and inhibit this enzyme. Potassium is also a necessary cofactor for sodium pump cycling. Severe hypokalemia (<2.5 mEq/liter) will reduce the rate at which the sodium pump turns over, in effect slowing the pump and exacerbating concomitant sodium pump inhibition due to cardiac glycosides. Also, chronic hypokalemia has been shown to reduce the number of Na^+,K^+-ATPase units in skeletal muscle,[27] but not in myocardium, thereby potentially decreasing the volume of drug distribution. Finally, hypokalemia probably has detrimental effects on cardiac electrophysiology that are separate from the toxic effects of digitalis. Although most of the electrophysiologic effects of hypokalemia have been studied in vitro or in animals, clinical experience suggests that such effects also occur in humans.

In contrast to hypokalemia, hyperkalemia will result in a further depolarization of myocardial conduction tissue, particularly in AV nodal tissue, where conduction is relatively slow, leading to an exacerbation of digitalis-induced conduction delays. Thus, potassium may exhibit a bimodal effect on AV conduction, depending on the extracellular concentration. In other words, hypokalemia may exacerbate digitalis-induced AV block, whereas hyperkalemia may worsen nodal conduction delays regardless of the cause. Therefore, potassium should be administered cautiously to any patient with first- or second-degree AV block, and facilities for external or transvenous cardiac pacing should be readily available. Potassium is most efficacious for the treatment of cardiac glycoside-induced ventricular arrhythmias and may be effective even when the serum potassium concentration is in the normal range.

Because potassium is one of the few therapies that has some specificity for digoxin intoxication, the routine administration of potassium supplements to digitalized patients receiving loop diuretics is probably justified. However, several classes of drugs that are often prescribed concurrently in these patients may raise the serum potassium concentration, including potassium-sparing diuretics, nonsteroidal anti-inflammatory drugs (NSAIDs), angiotensin-converting enzyme (ACE) inhibitors, and nonselective β blockers. Guidelines for administration of potassium salts to patients with proven or suspected digitalis toxicity are listed in Table IV.

Other electrolyte abnormalities may affect myocardial sensitivity to digitalis. Administration of magnesium (Mg^{2+}) salts suppresses some digitalis-induced arrhythmias. Hypomagnesemia, which is relatively common in patients receiving long-term diuretic therapy, appears to predispose to digitalis toxicity.[28,29] Nevertheless, the clinical importance of Mg^{2+} depletion in digitalis therapy remains uncertain. There is only a poor correlation between serum and tissue Mg^{2+} concentration, leaving unresolved the issue of whether blood Mg^{2+} levels are relevant to digitalis toxicity. In contrast, elevated serum Ca^{2+} levels increase ventricular automaticity, and this effect is at least additive to, and perhaps synergistic with, the effects of digitalis. Intravenous calcium should be administered cautiously to digitalized patients, since it may provoke clinically important ventricular arrhythmias.

Advanced age and renal insufficiency: Some consider advanced age a contributor to risk of digitalis toxicity, although it is difficult to dissociate it as an independent risk factor from many other factors that increase the likelihood of digitalis intoxication. Aside from the severity of any underlying heart disease, the gradual reduction in the glomerular filtration rate with age will necessarily predispose to digoxin accumulation. Digoxin's volume of distribution is also decreased in more advanced renal insufficiency, and thus the loading dose and maintenance doses will need to be adjusted downward accordingly.

Thyroid disease: In hypothyroid patients, the clearance rate of digoxin is consistently diminished. In those with hyperthyroidism, serum digoxin levels tend to be decreased, perhaps due to a direct effect of thyroid hormone to increase Na^+,K^+-ATPase density in many tissues, thus increasing digoxin's volume of distribution. The sensitivity of patients with thyroid disease to digitalis is a result of changes in target-organ responsiveness, perhaps in part due to altered autonomic tone, as well as changes in digoxin's pharmacokinetics.

Pulmonary disease: Respiratory failure and hypoxemia frequently provoke arrhythmias similar to those associated with digitalis excess. Excessive digitalis sensitivity in patients with pulmonary disease often correlates with overt right-sided heart failure, hypercapnia, and hypoxemia. The sympathomimetic agents commonly used in the therapy of chronic airways disease also increase the likelihood of digitalis-related arrhythmias.

Type and severity of underlying heart disease: Toxicity in otherwise healthy subjects who ingest large quantities of digitalis either accidentally or with suicidal intent is usually characterized by diminished AV conduction or by sinoatrial exit block, with little evidence of increased automaticity. In patients with ischemic heart disease, valvular heart disease or cardiomyopathies, the effects of digitalis often are superimposed on preexisting abnormalities of impulse formation and conduction. In addition, digoxin binding by amyloid fibrils may contribute to the increased sensitivity to cardiac glycosides that is characteristic of this cardiomyopathy.

In patients with underlying ischemic heart disease and left ventricular dysfunction, the net effect of digitalis administration on myocardial oxygen consumption is the result of two opposing actions of this class of drugs: an increase in contractility, which necessarily increases oxygen consumption, and an eventual decline in wall tension, which decreases oxygen uptake. In the failing heart, digitalis glycosides may increase cardiac output sufficiently to allow left ventricular end-diastolic pressure and volume to decrease gradually, resulting in a decline in myocardial wall tension. Thus, the frequency of angina pectoris has been observed to improve after digitalization in patients with decompensated heart failure, but not in patients who were initially well compensated and who did not have very elevated end-diastolic ventricular pressures. One study[30] reported improved myocardial perfusion judged by thallium-201 scans in response to digoxin in patients with coronary artery disease and left ventricular dysfunction. The combination of propranolol and digoxin was also found to be advantageous in a subgroup of patients with angina pectoris and abnormal ventricular function.[31]

TREATMENT OF DIGITALIS TOXICITY

The key to successful treatment is early recognition that an arrhythmia may be related to digitalis intoxication. The more common manifestations, such as occasional ectopic beats, first-degree AV block, or an accelerated junctional pacemaker in the setting of atrial fibrillation, require only temporary drug withdrawal, electrocardiographic monitoring (if indicated), and subsequent dosage schedule adjustment to prevent recurrences. Rhythm disturbances that impair cardiac output require more active intervention. Ventricular tachycardia due to digitalis intoxication demands immediate vigorous treatment. Sinus bradycardia, sinoatrial arrest, and AV block are sometimes treated effectively with atropine. Temporary pacing may be necessary. Nonparoxysmal AV junctional rhythms with rates >100 beats/min should be monitored closely and treated actively, at least in some patients.

Potassium: Both hypokalemia and hyperkalemia may exacerbate digitalis-induced arrhythmias. Hyperkalemia can occur as a consequence of massive digitalis overdose, usually following attempted suicide, but rarely complicates the more common forms of digitalis toxicity in patients with underlying heart disease, unless advanced renal insufficiency is also present (Table I). Potassium salts, as noted in Table IV, are indicated for ectopic ventricular arrhythmias, even when the serum potassium level is within the "normal" range. Potassium may also improve digitalis-induced AV block in the presence of hypokalemia, although it should be given cautiously, with concurrent cardiac monitoring.

TABLE V Relation of Pretreatment Hyperkalemia to Outcome in Digitalis Intoxication

Pretreatment Serum Potassium (mEq/liter)	Gaultier et al (1978)*			Antman et al (1990)†		
	Patients (n)	Deaths (n)	%	Patients (n)	Deaths (n)	%
< 5	42	1	2	30	1	3
≥ 5 ≤ 6.4	17	6	35	24	6	25
> 6.4	10	9	90	8	1	12.5

*Data from previous trial of conventional treatment by Gaultier M, Bismuth C. L'intoxication digitalique. *Rev Prat* 1978;28:4579.
†Treated with F(ab) fragments.
Reprinted with permission from *Circulation*.[32]

Digoxin-specific F(ab) fragments: The widespread availability of F(ab) fragments of high-affinity, polyclonal, digoxin-specific antibodies (Digibind, Burroughs Wellcome Co.) provides the clinician with a means of rapidly and selectively reversing digoxin toxicity with little risk of adverse effects. The use of F(ab) fragments, as opposed to intact IgG molecules, results in rapid clearance of the antibody fragment–digitalis complex, and also reduces the immunogenicity of this sheep protein. Digoxin-specific F(ab) fragments also have a large volume of distribution and result in rapid, and effectively irreversible, removal of digitalis from myocardial and other tissue-binding sites. Several thousand patients with life-threatening digoxin or digitoxin toxicity have now been treated, most successfully and with few adverse effects.[32,33] A few patients have now been treated more than once for suicidal digitalis overdose. To date, no evidence of serum sickness or serious reaction to the injection of this foreign (sheep) protein has been observed.

Recently, final results were reported from a multicenter prospective trial of the use of F(ab) fragments for treatment of acute, life-threatening digitalis toxicity,[32] and from an observational surveillance study of experience with antidigoxin F(ab) antibody fragment preparations following Food and Drug Administration approval and marketing.[34] Figure 1 shows the experience with F(ab) fragments given to 150 patients with severe digoxin or digitoxin intoxication. Patients ranged in age from neonates treated only hours after birth to 94 years. The median digoxin concentration before administration of the antidote was 8.0 ng/mL. As shown quantitatively in Figure 1, this was associated with high-degree AV block or severe ventricular arrhythmias, including ventricular fibrillation (in 33%) and asystole (11%). The median serum creatinine level was 2.8 mg/dL in adults, and 5 patients were receiving long-term hemodialysis therapy; 40% had normal renal function, and 90% of patients had a complete or partial response to F(ab) fragments of antidigoxin antibodies, with few adverse effects. Failure to respond (10%) was most often attributed to inadequate dosing, moribund clinical status before F(ab) fragment administration, or the likely absence of digitalis toxicity as the cause of the patient's symptoms. The most prominent adverse effect, seen in 4% of patients, was rapid development of hypokalemia, presumably due to sodium pump reactivation in skeletal muscle and other tissues following dissociation of digitalis from its binding site on Na^+,K^+-ATPase. Table V lists the results of treatment with F(ab) antibody

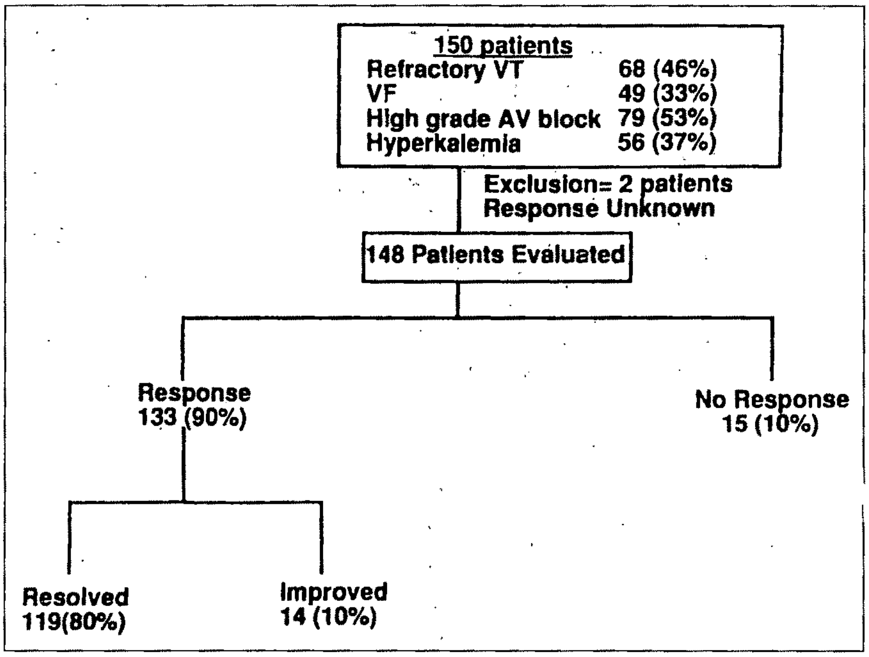

FIGURE 1. Clinical response to F(ab) fragment treatment in 150 patients with life-threatening digitalis intoxication.
VT = ventricular tachycardia;
VF = ventricular fibrillation;
AV = atrioventricular.
(Reprinted with permission from *Circulation*.[32])

fragments versus conventional treatment of digitalis poisoning in patients who had become hyperkalemic. Importantly, the mean time to an initial response was 19 minutes after initiation of the F(ab) fragment infusion, with a complete response obtained within 88 minutes on average. No allergic phenomena were witnessed in this study.[32]

In an observational surveillance study covering the first 2 years of postmarketing experience with F(ab) fragments of antidigoxin antibodies, information was received by the manufacturer (Burroughs Wellcome Co.) on 717 adult treatments, estimated to be about 15% of all treatments administered during this period.[34] Figure 2 shows the age distribution of those individuals diagnosed as having digitalis toxicity who were prescribed the F(ab) fragment preparation. The increased number of treated women >70 years of age reflects the increased survival rate of women in this age group, but it also may reflect the tendency of many clinicians to prescribe at a constant dose (e.g., 0.125 or 0.25 mg/day), which would lead to higher digoxin concentrations in women due to their lower lean body mass and lower absolute glomerular filtration rate.

Most patients who received antidigoxin F(ab) fragments in this observational study were demographically and clinically similar to those reported in the retrospective study of Mahdyoon et al.[9] Most patients had some degree of renal impairment and most were normokalemic. The median digoxin serum concentration at the time of diagnosis of digitalis intoxication was 4.2 ng/mL, similar to that reported by Mahdyoon et al[9] in a similar patient population (Table I). The type and frequency of arrhythmias are shown in Figure 3 for patients with and without underlying heart disease. The response rate was not as high as that reported in the prospective trial,[9] presumably due in large part to the much more heterogeneous patient population in the postmarketing trial.[34] The nonresponse rate was 14% in patients who developed suspected digoxin toxicity while receiving maintenance doses of the drug, 20% in patients who were receiving loading doses of digoxin or who were in the hospital during development of suspected digoxin toxicity, and 15% in patients with heart disease who had ingested a single large overdose. Importantly, there were no nonresponders in the group of patients without underlying heart disease who had ingested a single large dose. The reasons for the absence of any response to F(ab) fragments in some cases of suspected digoxin toxicity were again similar to those described for nonresponders in the prospective trial by Mahdyoon et al[9]: inadequate dosing, moribund clinical status, or incorrect diagnosis.[34]

The postmarketing surveillance trial also provides a better assessment of the complications likely to be seen in the treatment of suspected digitalis toxicity in clinical practice.[34] These data were discussed in greater depth in a recent symposium.[35–41] The number of adverse events associated with F(ab) fragment administration was low (7%) and included allergic-type responses,[36] possible recrudescence of digitalis toxicity, and other events, such as worsening of CHF symptoms due to the abrupt withdrawal of the cardiac glycoside's inotropic effects. Interestingly, the abrupt onset of hypokalemia, which occurred more frequently in the prospective trial of patients following massive ingestion of digoxin or digitoxin, was not observed in this patient population. Only 6 of 717 patients (0.8%) had probable allergic reactions to F(ab)

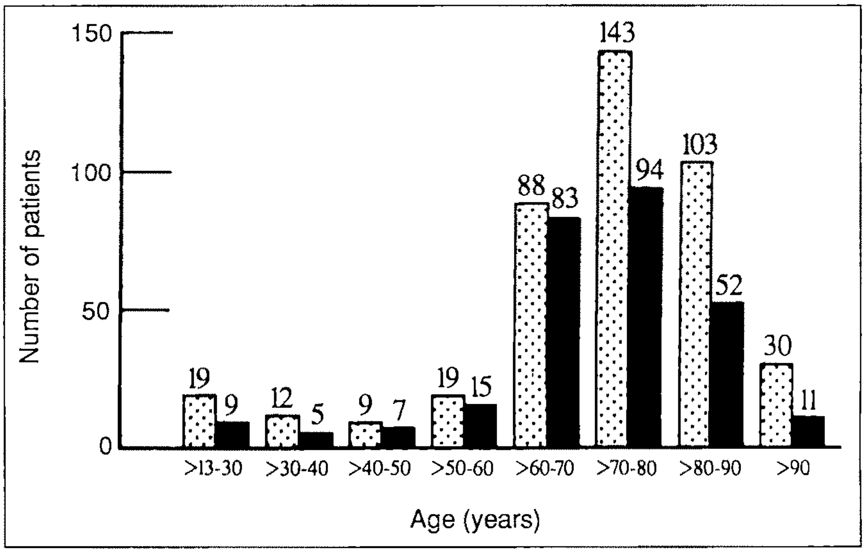

FIGURE 2. Distribution by age and gender of 717 patients receiving F(ab) fragments of antidigoxin antibodies in a postmarketing surveillance study. (Reprinted with permission from *J Am Coll Cardiol*.[34])

antibody fragments, characterized by pruritic rash and flushing or facial swelling, all of which responded to symptomatic treatment.[36] There was a greater likelihood (5%) of an allergic response if a patient had a history of allergy or asthma; in patients with no history of allergy or asthma the incidence of allergic response was 0.3%. Recrudescent digitalis toxicity occurred in 2.8% of patients receiving F(ab) fragments, with recurrent symptoms developing most commonly within 3 days of therapy.[34] The most common reason was inadequate dosing, based on the full neutralizing dose calculated using the formula and nomogram in the product's approved labelling. Interestingly, 18% of the patients studied were restarted on digitalis therapy at a median of 7 days after administration of F(ab) fragments. In 2 patients who were prescribed digoxin for ventricular rate control in chronic atrial fibrillation 1 day and 4 days after F(ab) antidigoxin antibody fragment administration, the drug was initially ineffective in slowing ventricular response, presumably due to persistent, effective neutralizing antibody levels not yet excreted.

Neither this observational surveillance study nor any prospective trial to date has addressed the utility of F(ab) fragments of antidigoxin antibodies for diagnosing digoxin intoxication. No clinical trials are under way to evaluate the utility and safety of F(ab) antidigoxin fragments in the diagnosis and treatment of suspected digitalis toxicity of mild-to-moderate severity. This is in part due to the low incidence of digoxin toxicity in digitalized patients, as already noted. Nevertheless, the unique specificity of the antibody preparation and its good safety record in more seriously intoxicated patients make a case for its administration to patients with suspected moderate degrees of digitalis intoxication. A few patients have received the preparation more than once, usually in the setting of reported suicidal ingestion, without incident. There are too few data, however, to comment on its safety when administered to a given patient on >1 occasion, as would likely occur with routine diagnostic use. A more attractive approach, feasible with currently available recombinant DNA technology, would be to develop a nonallergenic F(ab) fragment with "framework" regions of human immune specificity that could be used without fear of patient sensitization.

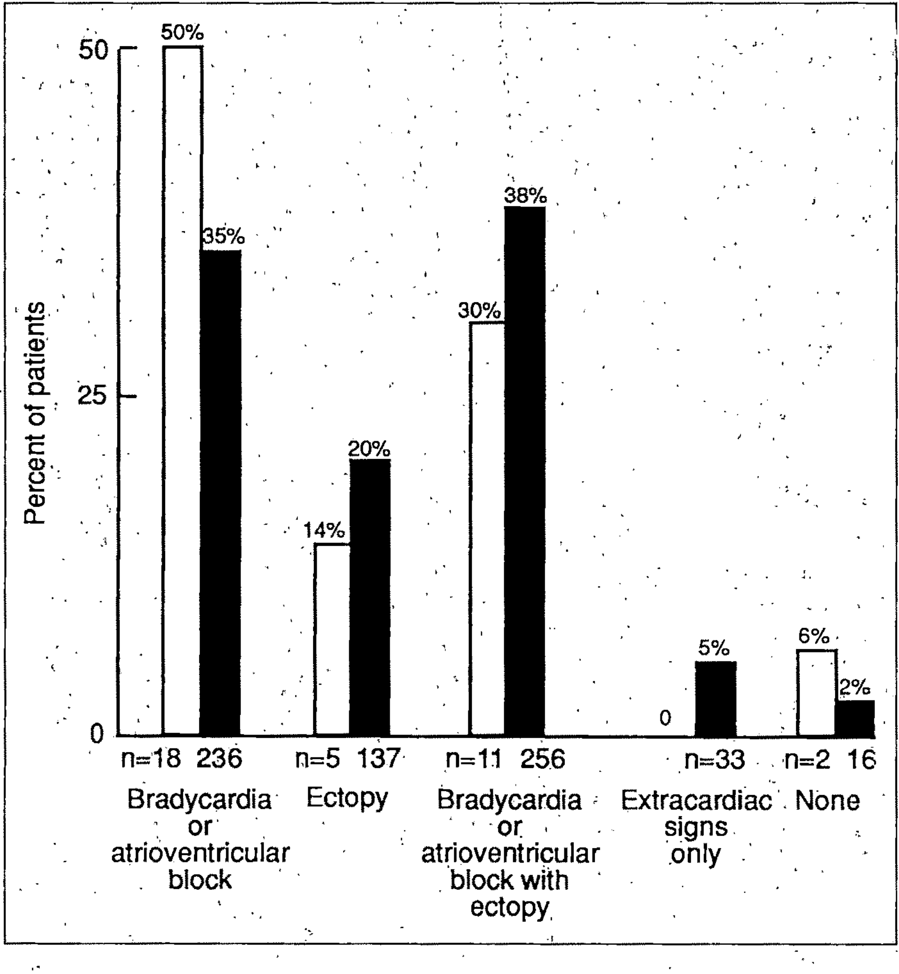

FIGURE 3. Selected signs of digitalis intoxication in 717 patients reported in a post-marketing surveillance study of the use of F(ab) fragments of antidigoxin antibodies, by presence (*closed bars*) or absence (*open bars*) of heart disease. (Reprinted with permission from *J Am Coll Cardiol*.[34])

The potential immunogenicity of the present F(ab) formulation and its relatively high cost ($1,140.00 as of August 1991 in a representative hospital) argue against its routine use in the diagnosis of suspected digoxin intoxication. If the clinician's index of suspicion for digoxin toxicity is sufficiently high, and the observed cardiac arrhythmia sufficiently serious to warrant a major intervention, such as insertion of a temporary pacemaker, administration of F(ab) fragments of antidigoxin antibodies would be indicated. If an electrocardiographic abnormality is due to digoxin toxicity, most patients should show some response within 20–40 minutes after beginning a 40 mg infusion. If a response is observed, the full neutralizing dose of F(ab) fragments should be given to prevent recrudescent toxicity. Digoxin could then be safely reinstituted at a lower dose, if indicated, within several days.

Antiarrhythmics: The drugs most useful for treatment of digitalis-induced ventricular arrhythmias, aside from F(ab) fragments of antidigoxin antibodies and potassium, are lidocaine and phenytoin, each of which has little effect on the sinus node or on sinoatrial, AV, or His–Purkinje conduction. Phenytoin may occasionally improve sinoatrial or AV conduction. Both quinidine and procainamide depress AV and sinoatrial conduction and may exhibit proarrhythmic effects in the presence of digitalis-toxic arrhythmias. Quinidine also reduces tissue binding and renal clearance of digoxin, thus altering both volume of distribution and elimination half-life. Beta blockers may also exacerbate AV conduction disturbances due to digitalis, but they are clearly effective in decreasing catecholamine-induced automaticity and in shortening the refractory period of atrial and ventricular muscle while slowing conduction velocity. Use of an ultra-short-acting β blocker, such as esmolol, may be appropriate initially, when the possibility of worsening AV block or a negative inotropic effect exists, particularly in severely ill patients.

Electrical cardioversion: In the absence of severe digitalis-induced arrhythmias, direct current cardioversion is safe, particularly if lower energy levels are used. Electrical cardioversion is potentially hazardous in severe arrhythmias with advanced digitalis toxicity and should be avoided if other measures are available and effective.

Binding resins and hemodialysis: Selected cardiac glycosides such as digitoxin, which undergo some enterohepatic circulation, may be trapped by binding resins during transit through the gut lumen. Both cholestyramine and colestipol can reduce serum digitoxin concentrations by this means, but the decrease is not of sufficient magnitude or rapidity to affect life-threatening toxicity. Hemodialysis is ineffective both in the case of digitoxin toxicity, due to its extensive binding by serum proteins, and in the treatment of digoxin toxicity, due to that drug's large volume of distribution. It could be used to control life-threatening hyperkalemia if digoxin-specific F(ab) fragments were unavailable.

CONCLUSION

As the role of digitalis glycosides becomes better defined in the modern pharmacotherapy of cardiovascular disease, and with the availability of an accurate and reliable digoxin assay, both the incidence and mortality of digitalis intoxication have declined markedly over the past 2 decades. Nevertheless, the documentation of digitalis toxicity in most clinical settings remains difficult, due to the varied and nonspecific nature of the signs and symptoms of digitalis intoxication. The development and widespread availability of F(ab) fragments of antidigoxin antibodies provide the clinician with a useful and effective therapy for patients with potentially life-threatening digitalis-induced toxic rhythm disturbances.

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DISCUSSION

Dr. Gheorghiade: It can be very costly to rule out digoxin intoxication. At our institution, if a patient has complete atrioventricular (AV) block and a serum digoxin concentration of ≥ 2 ng/mL, we keep the patient hospitalized for several days, after which we decide whether the AV block was related to digoxin therapy. In several cases we have had to implant a pacemaker 1–2 weeks later.[1]

More recently, we have used digoxin-specific F(ab) fragments to diagnose and treat digoxin intoxication. This may reduce the cost of hospitalization and reduce the length of stay.[2]

Dr. Kelly: Compared with several days in the intensive care unit (ICU), the cost of Digibind therapy is competitive. That puts the cost in perspective. I think today there is good reason to give Digibind to a patient in whom one strongly suspects digoxin intoxication and whose serum digoxin level is ≥ 2 ng/mL, for just the reasons you mentioned.

Dr. Gheorghiade: Do you think it would be reasonable to use digoxin-specific F(ab) fragments in clinical practice to rule out digoxin intoxication?

Dr. Kelly: If it saves admission to the ICU—if one could make that decision in the emergency department. For example, if there is no change in the electrocardiogram or in serum potassium measurements following an adequate dose of F(ab) fragments, digoxin toxicity is made much less likely. In many hospitals, it may take several hours to arrange for and facilitate admission to a coronary care unit. By that time, according to results of an observational study,[3] every patient would have shown a response to F(ab) fragment therapy, and probably could have been treated in the holding unit if digoxin intoxication were suspected.

Dr. Leier: In the recent study[4] that examined the effects of F(ab) fragments in patients with digoxin intoxication, it appears that there is a tremendous predisposition toward digoxin toxicity in women >70 years of age. Dr. Kelly, what are your thoughts about this?

Dr. Kelly: The most immediate issue that comes to mind is that of lean body mass. Most patients are given a common dose of digoxin, and due to the lower lean body mass and lower glomerular filtration rate in women, steady-state serum drug levels would be higher, thus predisposing to toxicity.

Dr. Creager: How often is hyperkalemia observed in nonsuicidal digoxin-toxic patients?

Dr. Kelly: It is very unusual. Generally, you will not see it in patients with serum digoxin levels of 3–4 ng/mL; you will see it at levels of 8–10 ng/mL. Actually, hypokalemia—not hyperkalemia—is more common in patients who have not taken a suicidal overdose.

Dr. Gheorghiade: Patients with severe heart failure and a low cardiac output may have an unexpectedly high serum potassium in the presence of a relatively low serum digoxin concentration. Factors like prerenal azotemia and diabetes mellitus increase the likelihood of its occurrence.[5]

Dr. Kelly: If these patients have metabolic acidosis, they will also become hyperkalemic.

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Current Status of Non-Digitalis Positive Inotropic Drugs

Carl V. Leier, MD

Considerable effort and resources have been directed at the development and study of positive inotropic drugs over the past 10–15 years. Much has been learned about the physiology and pharmacology of myocardial contraction, the application of agents to augment contractility, and, importantly, the general and specific limitations of positive inotropic therapy. Studies on acute inotropic intervention have now shown that a drug's ability to augment overall cardiac performance is heavily dependent on its effects on vasculature, vascular control, and ventricular–vascular coupling. The clinical research on new agents has served to remind us how difficult it is to formulate the "ideal" positive inotropic or cardiovascular support drug for the critical care setting.

The vast effort to develop a chronically and orally administrable drug to replace or even supplement digitalis has generally been disappointing. The dopaminergic agents (e.g., ibopamine, levodopa) act primarily via vasodilation and their effectiveness and role in managing heart failure remain unresolved. The initial excitement about the phosphodiesterase III inhibitors (e.g., amrinone, milrinone, enoximone) has been tempered by the results of large well-designed trials indicating variable effectiveness and a prominent adverse effect profile. During long-term oral administration none of these agents has been shown to improve clinical status or exercise capacity beyond that achieved by digoxin, when administered either separately or in combination with digoxin. The Prospective Randomized Milrinone Survival Evaluation (PROMISE) trial, showing that repeated oral administration of milrinone can increase mortality in heart failure, is having a devastating effect on the further development of this class of drugs.

Investigation is proceeding at basic levels to unravel the intricate mechanisms of myocardial contraction and we are beginning to see the results of this research. Agents have been developed to "sensitize" the contractile apparatus to calcium and to act in very precise locations. We are hopeful that some of these agents will have a favorable benefit to adverse effect ratio and earn a position in the clinical therapeutics of heart failure.

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The last 10–15 years have witnessed a considerable amount of research on positive inotropic drugs, which has contributed greatly to our understanding of the pharmacodynamics of myocardial contraction. New drugs have been developed for acute, short-term positive inotropic intervention (e.g., milrinone, dopexamine), and considerably more has been learned about the complex mechanisms of standard inotropic therapy (e.g., dopamine, dobutamine). Certainly, we learned that the formulation of the "ideal" positive inotropic drug is most difficult, with many attempts failing because of ineffectiveness or toxicity. The huge investment of money, time, manpower, and other resources to develop an orally administrable positive inotropic drug to supplement or replace the digitalis glycosides has not yet been rewarded. Although the question of whether long-term positive inotropic therapy can ever render more beneficial than adverse effects remains unanswered, laboratories are continuing to explore the intricate mechanisms of contraction and to formulate more precise and sophisticated means of improving myocyte function and overall myocardial performance.

ISSUE OF CLASSIFICATION

There are a number of ways to classify positive inotropic drugs. Classification on the basis of their precise cellular mechanisms serves basic research laboratories quite well. Classification on the basis of whether an agent does or does not increase cyclic adenosine monophosphate (AMP) is useful for basic laboratories but has little value in clinical medicine. Of course, one can generally classify

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positive inotropic drugs as either digitalis or nondigitalis agents, but this classification is of limited value for both basic and clinical study. The positive inotropic drugs can be clinically separated into those used for acute and long-term administration; this classification is useful clinically, but has little utility in basic laboratories. For now, I prefer the classification presented in Table I, which is generally accepted and incorporates the major clinical and laboratory considerations.

TABLE I General Classification of Positive Inotropic Agents and Overview of Their Current Status for Positive Inotropic Intervention

	Clinical Application as Positive Inotropic Therapy	
Positive Inotropic Drug Groups	Acute/ Short-Term	Long-Term
Digitalis	+	+
Catecholamines and related compounds		
β-adrenergic agonists	+	–
α-adrenergic agonists	–	–
Dopaminergic agents	+ (dopamine)	Unlikely
Phosphodiesterase inhibitors	+	Unlikely
Others		
Direct adenylate cyclase agonists	?	?
Calcium sensitizers	?	?
H_2-receptor agonists	?	?
Endogenous substances (glucagon, thyroid hormone)	?	?

This article will follow the general format of Table I. It is not my intent to provide a comprehensive review of positive inotropic therapy. Such a treatise is available elsewhere.[1] Digitalis glycosides will be reviewed in other articles in this supplement. New information on the clinical pharmacology of the catecholamines and related compounds will be discussed. The agents proposed over the past 10–15 years for long-term positive inotropic therapy will be reviewed with an emphasis on the critical studies influencing their development, approval, and clinical application.

CATECHOLAMINES AND RELATED COMPOUNDS

The introduction of dobutamine for acute inotropic intervention in the late 1970s filled a void in the therapeutic spectrum of catecholamines/catechols available in the critical care setting. This drug group now includes agents with a wide range of vascular activity, extending from very strong vasopressor properties, such as norepinephrine, to those with very significant vasodilating effects, such as isoproterenol. Although low-dose dopamine may have some vasodilating properties, moderate- to high-dose dopamine elicits a significant amount of vasoconstriction via α_1-adrenergic receptor agonism. With a pharmacologic profile to deliver a considerable amount of positive inotropy to enhance cardiac contractility, stroke volume and cardiac output with a relatively modest peripheral vascular response, dobutamine landed nicely between dopamine and isoproterenol. Physicians in critical care units now have a reasonable choice of compounds for acute inotropic intervention.

The vascular properties of dobutamine and dopamine: Dopamine and dobutamine are the catecholamines most commonly used in intensive cardiac care. Dobutamine is generally regarded as a primary positive inotropic drug and dopamine in standard doses as a vasopressor with positive inotropic effects. Recent studies have enhanced our understanding of the clinincal pharmacology of these two commonly used drugs.[2,3] Dobutamine reduces characteristic aortic impedance and dopamine does not. Dobutamine reduces wave reflectance with a later occurrence of the reflected wave, whereas dopamine evokes little change or an opposite effect on this parameter of vascular load. It has long been known that dobutamine consistently reduces vascular resistances and dopamine at moderate to high doses has little or the opposite effect on vascular resistances.

In terms of ventricular–vascular coupling, the aforementioned vascular properties of dobutamine greatly favor augmentation of myocardial contraction, stroke volume, and cardiac output and those of dopamine favor development of a vasopressor response with resultant increase in systemic blood pressure. Dobutamine does not alter the ratio of pulsatile to total power, whereas dopamine tends to increase this ratio, suggesting that the power and energy transfer for dobutamine is generally delivered in an augmented stroke volume and cardiac output (enhanced systemic flow) and that of dopamine in the delivery of pulsatile flow–pressure and enhanced systemic pressure. These studies indicate that positive inotropic intervention must be matched with appropriate vascular responses and ventricular–vascular coupling to optimize the positive inotropic potential of an agent. Basically, favorable ventricular–vascular coupling augments ventricular performance and forward flow, whereas unsatisfactory coupling can greatly negate a compound's positive inotropic effect. Stated another way, for any amount of positive inotropy delivered, the overall response in cardiac performance, stroke volume, and cardiac output will depend greatly on the effects the agent has on characteristic aortic impedance, wave reflectance, and peripheral vascular resistance.

The importance of the vascular properties of a positive inotropic drug in relation to its effects on overall cardiac performance has been demonstrated in another way for dobutamine using the calf Jarvik 7 artificial heart model.[3] In this mechanical heart model, racemic dobutamine in doses of 6–24 μg/kg/min increased cardiac output 10–15% while decreasing systemic and pulmonic vascular resistances. Right atrial pressure increased 20–40%, suggesting that the cardiac output increase was perhaps driven by dobutamine's vascular effects, shifting blood flow and volume centrally. Both enantiomers of dobutamine augment cardiac output in this model, but through different mechanisms. The dextroisomer increased aortic and central blood flow by greatly reducing systemic vascular resistance and characteristic aortic impedance; this is likely mediated by the β_2-adrenergic agonistic properties of D-dobutamine. The levoisomer of dobutamine increased central blood flow by enhancing venous flow; this appeared to be the result of a reduction in venous capacitance mediated by postsynaptic α-adrenergic receptor agonism of L-dobutamine. Therefore, it appears that in the artificial heart model, and likely in the intact human system as well, a considerable portion of the favorable central hemodynamic effects of dobutamine occur via its peripheral vascular properties.

Role of mitral regurgitation in the central hemodynamic response to dobutamine: A number of other factors are important variables in the overall cardiac response to the administration of a positive inotropic drug. Keren et al[4] demonstrated that a major component of stroke volume increase and pulmonary capillary wedge pressure reduction during dobutamine administration to patients with dilated cardiomyopathy and congestive heart failure (CHF) is attributable to a sizable reduction in the degree of mitral regurgitation. In patients with severe CHF, they found that dobutamine increased forward stroke volume approximately 40% and reduced pulmonary capillary wedge pressure to a similar degree while reducing the mitral regurgitant volume by approximately 50%. The reduction in mitral regurgitant volume is likely related to dobutamine's systemic vascular effects and afterload-reducing properties, which act to reduce ventricular volume and the size of the mitral valve's regurgitant orifice.

Dopexamine: Dopexamine is a new formulation in the catecholamine drug group. It was specifically designed to enhance myocardial contractility, stroke volume and cardiac output, to reduce systemic vascular resistance and ventricular afterload, and to augment renal and visceral blood flow. Dopexamine primarily stimulates β_2-adrenergic receptors with mild β_1-adrenergic and dopaminergic (DA1 and DA2) agonism.

In humans with severe CHF, dopexamine augments cardiac output at doses ≥0.25 μg/kg/min; this is achieved by an increase in stroke volume at the same dose level, and an increase in heart rate at doses ≥0.50 μg/kg/min.[5] Dopexamine reduces pulmonic and systemic vascular resistances and right- and left-sided heart filling pressures. Systemic diastolic blood pressure may decrease at doses ≥0.25 μg/kg/min, with some reduction in pulmonic diastolic pressures at doses ≥1.0 μg/kg/min. The overall improvement in ventricular performance during dopexamine infusion in CHF appears to be secondary to a positive inotropic response and systemic vasodilation (afterload reduction). Comparable findings have been reported by others.[6–10]

The regional hemodynamic effects of dopexamine are a result of vascular dopaminergic and β_2-adrenergic agonism.[5] Dopexamine generally lowers hepatosplanchnic vascular resistance and enhances hepatosplanchnic blood flow. Upper limb vascular resistance decreases with dopexamine, but with little change in limb blood flow because of a concomitant decrease (albeit mild) in systemic blood pressure and preferential vasodilation of other regions (e.g., hepatosplanchnic, renal). Dopexamine also lowers renal vascular resistance and tends to evoke a mild increase in renal blood flow at mean doses of ≥0.90 μg/kg/min. With respect to renal function, dopexamine may evoke a mild increase in urine output and urine sodium excretion.[5] It is important to note that as the dopexamine infusion is increased to doses >2 μg/kg/min, the augmentation in regional blood flow may decline.[5] Differences in infusion rates explain some of the disparity between the results of various studies examining dopexamine effects on regional blood flow and organ function.[5,10]

The exact role of dopexamine as an acute/short-term cardiovascular intervention remains to be determined. It does not have any obvious advantages in terms of central hemodynamic effects over currently available agents. The positive chronotropic response is not a particularly favorable feature. The rather prominent systemic vasodilatory effects will probably restrict dopexamine's use to patients with very high systemic vascular resistance and adequate systemic blood pressure. Dopexamine's ability to augment hepatosplanchnic blood flow may be useful, but it has not yet been determined whether dopexamine will improve the clinical condition of patients with compromised hepatosplanchnic blood flow. The ability to enhance renal blood flow and renal function is also a favorable feature, but it remains to be determined whether dopexamine has any advantage in these effects over those achieved by dopamine in low-to-moderate doses or by dobutamine in simply increasing cardiac output in low output states.

Other considerations: The development of pharmacodynamic tolerance, prominent side effect profile, and general lack of clinical benefit have virtually eliminated the use of orally administered β-adrenergic agonists from the long-term management of CHF; pirbuterol, butopamine, and prenalterol are examples of compounds in this group. Most CHF investigators are also not convinced that α-adrenergic agonism evokes enough positive inotropy to warrant consideration in the management of CHF. In addition, the vascular response to postsynaptic α-adrenergic agonism will not have a favorable effect on ventricular–vascular coupling and the effort to augment ventricular performance.

DOPAMINERGIC AGENTS

Some drugs in this group are worthy of comment because they are often placed under the category of "positive inotropic drugs." Dopaminergic drugs generally evoke vasodilatory responses by stimulating postsynaptic DA1 receptors and presynaptic DA2 receptors. Most of the cardiac effects, therefore, of dopaminergic drugs in the setting of CHF probably occur through preload and afterload reduction. Agents with predominant adrenergic and milder dopaminergic effects, namely, dopexamine and dopamine, were previously discussed.

Levodopa: Levodopa is decarboxylated after gastrointestinal absorption to form circulating dopamine. Whitsett and Goldberg[11] demonstrated a mild positive inotropic effect for levodopa in patients with Parkinsonism. In patients with CHF, levodopa at a dose of 1.5–2 g orally appears to evoke a modest increase in cardiac output and stroke volume and a mild-to-moderate reduction in systemic vascular resistance.[12–14] Oral administration of levodopa is accompanied by an increase in circulating dopamine levels[15] and, presumably, the hemodynamic responses to levodopa are then evoked by stimulation of myocardial β_1-adrenergic receptors and vascular dopaminergic receptors. Small, uncontrolled and nonblinded studies suggest that levodopa may be useful in the long-term management of chronic CHF,[15–17] but this possibility has not yet been challenged with a well-designed trial.

Ibopamine: Ibopamine was specifically designed to deliver a dopamine congener to the circulation. Ibopamine is converted after absorption to N-methyldopamine (epinine).

In the setting of CHF, ibopamine, at initial orally administered doses of 100–600 mg, evokes a modest positive inotropic response.[18,19] At 1–6 hours after administration, systemic and pulmonic vascular resistances decrease 5–20% below baseline. Cardiac output and stroke volume increase modestly over 4 hours after dosing, while heart rate either does not change or tends to increase slightly. We have demonstrated that ibopamine has a rather unusual hemodynamic profile in patients with CHF.[18,19] Between 15 and 60 minutes after administration, ventricular filling pressures and pulmonic arterial pressure tend to increase; then these pressures and systemic and pulmonic vascular resistances generally decrease. The mechanisms for this biphasic effect have not been clearly established, but it is not a particularly favorable one from a clinical perspective.

With respect to ibopamine's renal dopaminergic properties, several studies have shown that it may favorably affect overall renal function with enhancement of water and sodium clearance.[20–24] Long-term ibopamine administration may also be associated with a reduction in plasma renin activity and norepinephrine levels, presumably via presynaptic DA2 agonism.[24–26]

A number of ibopamine's properties are likely to keep it from becoming widely used in the management of CHF. These include a relatively brief duration of action for the doses recommended (50–300 mg),[18,19] biphasic hemodynamic response,[18,19] attenuation of hemodynamic effect with long-term dosing,[25] and impairment of ventricular diastolic function in select patients.[27] Nevertheless, a number of reports suggest that long-term ibopamine administration is capable of improving symptoms and perhaps exercise capacity in patients with CHF.[23,25,28–33] It is likely that most favorable clinical responses to ibopamine in CHF are mediated through its renal properties, rather than positive inotropy. Whether ibopamine will eventually earn a role in the long-term management of CHF patients will depend on the performance and results of large, appropriately designed multicenter trials. The effect of ibopamine on survival in CHF has not been examined.

TABLE II Subgroups of Major Phosphodiesterase III Inhibitors

Bipyridine derivatives
Amrinone
Milrinone
Imidazole derivatives
Enoximone
Piroximone
Benzimidazole derivatives
Sulmazole
Pimobendan
Adibendan

PHOSPHODIESTERASE INHIBITORS

The recent history of the development of phosphodiesterase inhibitors for CHF has been interesting, but rather disappointing. These agents were formulated to provide orally administrable positive inotropic therapy in the long-term management of CHF (Table II). The initial studies were quite encouraging in this regard[16,34–39] and created tremendous excitement among the pharmaceutical industry, investigators, and cardiologists. This initial enthusiasm began to wane when various centers reported concerns about effectiveness, frequent and significant adverse effects, and unfavorable influence on survival.

Amrinone: A number of reasonably well-performed studies have shown that the long-term oral administration of amrinone elicits a considerable number of intolerable or serious side effects combined with limited clinical effectiveness.[15,17,40–42] Although the orally administered form of amrinone was withdrawn from further development, the intravenous preparation was approved for clinical use. It is important to note that unless amrinone is administered at initial high infusion rates (30–40 μg/kg/min) or by initial high-dose bolus, it does not elicit a positive inotropic response.[43–48] Amrinone infusions starting at doses of 10 μg/kg/min evoke a significant decrease in systemic and pulmonic vascular resistances and ventricular filling pressures.[43–48] Stroke volume and cardiac output increase in response to afterload reduction. Clinically, amrinone should probably be avoided in patients in whom systemic blood pressure is substantially depressed and systemic vascular resistances are not elevated.

Milrinone: The development of milrinone and its pilot clinical investigations came soon after amrinone's introduction. Both are members of the bipyridine family of phosphodiesterase inhibitors (Table II). In contrast to amrinone, whose precise mechanisms of action have not yet been fully elucidated, milrinone acts predominantly through phosphodiesterase III inhibition. By preventing the breakdown of intracellular cyclic AMP, milrinone, like the other phosphodiesterase III inhibitors, elicits a myocardial positive inotropic response and vascular relaxation. Both oral and intravenous preparations reduce systemic and pulmonic vascular resistances and ventricular filling pressures and augment stroke volume and cardiac output. The improvement in ventricular performance is believed to be related to a combination of afterload reduction and positive inotropic response.[49–61] Milrinone may also have a favorable effect on ventricular diastolic function.[61] The prolonged half-life of serum concentrations and of cardiovascular effects make milrinone a less-than-ideal acute positive inotropic intervention.

Two studies have virtually abolished any role for oral milrinone in the long-term therapy of CHF. A large multicenter trial comparing placebo, digoxin, milrinone, and combination milrinone–digoxin demonstrated that digoxin, milrinone, and the combination generally improved symptoms and increased exercise capacity over a 12-week study period versus placebo.[62] Milrinone, alone or combined with digoxin, did not demonstrate any clinical or exercise response advantage over that achieved by digoxin alone and also elicited more adverse effects, particularly ventricular ectopy. The multicenter Prospective Randomized Milrinone Survival Evaluation (PROMISE) trial, involving >1,000 patients in NYHA functional classes III and IV, taking standard long-term therapy, demonstrated that the addition of milrinone had an unfavorable effect on survival with little to no demonstrable clinical benefit versus placebo.[63] The functional class IV CHF patients experienced >50% increase in mortality while receiving long-term milrinone versus placebo-treated patients. This is a very important observation because patients with functional class IV CHF are those who would most likely have been considered clinical candidates for long-term oral milrinone therapy.

Oral milrinone was withdrawn from further study, and it is uncertain whether its developer is interested in marketing the intravenous preparation to compete against its own compound, intravenous amrinone.

Enoximone: Enoximone, an imidazoline derivative, is another phosphodiesterase inhibitor developed for short- and long-term management of CHF. The general hemodynamic effects are very similar to those of milrinone.[64–79] The expectation that enoximone would be an effective, long-term oral positive inotropic drug vanished when well-designed trials showed that it generally does not improve clinical status and exercise capacity above that attained with long-term placebo administration.[80,81] The results of a number of nonblinded, uncontrolled studies have suggested that enoximone may adversely affect survival.[74,76,81,82]

The congeners of enoximone (e.g., piroximone) do not appear to offer any hemodynamic or clinical advantage over that delivered by enoximone.[83–85]

Benzimidazole derivatives: The precise cellular mechanisms of this group of compounds have not been fully elucidated. Experimental data suggest that these agents evoke phosphodiesterase inhibition and also "sensitize" the myocardial contractile apparatus to calcium ions. Sulmazole, pimobendan, and adibendan are examples of this group of compounds.[86–91] It is uncertain whether the feature of "calcium sensitization" or any other cellular mechanism of the benzimidazole derivatives will sustain these agents beyond the rather dismal future for phosphodiesterase inhibition alone. The hemodynamic responses to this group of drugs are quite similar to those described for other phosphodiesterase inhibitors. Preliminary reports of open-label, noncontrolled or small-population studies of long-term pimobendan administration in CHF are somewhat encouraging.[87–90]

Other phosphodiesterase inhibitors: Many other phosphodiesterase inhibitors have been formulated in response to the early period of excitement over the development of this drug group for CHF therapy. Examples include CI-914, CI-930, ICI-153, 110, RO 13–6438, D 13625, R 80122, and RS-1893. At this point, most of these compounds have been withdrawn from clinical development.

Other compounds: A few other agents deserve comment because of unique mechanistic properties or potential clinical application. Forskolin directly stimulates sarcolemmal adenylate cyclase, thereby bypassing the β-adrenergic receptor in the generation of cyclic AMP. Thus, it may not be vulnerable to β-adrenergic receptor down-regulation.[92] Forskolin augments myocardial contractility, stroke volume, and cardiac output while reducing ventricular filling pressures and vascular resistances; however, it may also evoke clinically significant hypotension and tachycardia.[92,93]

DPI 201–106 appears to be the prototype for a group of drugs designed to sensitize the contractile apparatus to calcium. Via this mechanism, DPI 201–106 augments myocardial contractility and cardiac performance.[94–96] DPI 201–106, 80–100 mg administered orally to patients with chronic CHF, results in an increase in mean cardiac output of 20–25% and stroke volume of 25–30%. Left ventricular filling pressures may decline modestly. This compound may also evoke systemic vascular dilation. Because calcium sensitization should actually enhance vasoconstriction, the mild smooth muscle-relaxing effect has been attributed to some calcium channel antagonism.[94]

OPC-8212 appears to enhance myocardial contractility through a number of mechanisms, including phosphodiesterase inhibition, increase in intracellular sodium ions and enhanced opening of calcium channels.[97,98] Preliminary reports suggest that it has relatively modest hemodynamic effects, but whether these effects persist with long-term administration is not yet determined.[99,100] However, the clinical and exercise responses of long-term OPC-8212 administration in CHF are somewhat encouraging.[100–102] Kubo et al[100] noted a significant reduction in the frequency of ventricular ectopic beats during 4 weeks of OPC-8212 therapy in CHF patients.

CONCLUSION

For acute positive inotropic intervention, dobutamine and dopamine have retained their positions as first-line agents despite the development of newer drugs. It is unlikely that this situation will change significantly in the next few years.

The results of several multicenter trials of various phosphodiesterase inhibitors have had a devastating effect on the development of cardiotonic drugs. Although the investigations principally dealt with the mechanism of phosphodiesterase inhibition, the caution and concern engendered have now been extended to include all agents that increase cyclic AMP and to the whole concept of positive inotropic intervention. Disturbingly, the entire concept of long-term positive inotropic therapy, irrespective of mechanism involved, is in jeopardy because of unfavorable results of one or perhaps two positive inotropic subgroups. On the other hand, much evidence suggests that positive inotropy alone is not a reasonable approach to the long-term management of CHF. For long-term positive inotropic intervention to be successful, it will have to possess at least two additional desirable properties, including a favorable effect on peripheral vasculature and ventricular–vascular coupling, few adverse effects, improved clinical course or survival, augmentation of subendocardial blood flow and myocardial perfusion, favorable myocardial energetics, reparative effects on cardiomyocytes, vascular/skeletal muscle conditioning, and organ or region specificity. Short of this, the inotropic agent will do no more than "beat a tired, dying horse."

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DISCUSSION

Dr. Lewis: It is very difficult to quantitate, but when digoxin and dobutamine are compared in the acute state, despite their being almost equal in inotropic effect, dobutamine consistently increases cardiac output more. One has to wonder whether this difference is attributable to the venous effect of dobutamine versus digoxin. Dr. Leier, do you have any comment on this?

Dr. Leier: We have been trying to distinguish the arterial and venous effects of dobutamine as well. In the calf Jarvik 7 artificial heart model,[1] we removed the whole heart except for vestiges of atria and looked at the enantiomers of dobutamine. Actually, we began the study by delivering racemic dobutamine to this model. We found that cardiac output and stroke volume increased and were a bit surprised by these findings, considering this was a mechanical heart model.

We subsequently investigated the enantiomers. The dextroisomer was found to induce considerable peripheral dilation; perhaps it delivers more flow centrally via that mechanism. The levoisomer appeared to have more of an α agonist effect on the venous system than we ever saw in the arterial system, which I found very interesting. We saw a tremendous reduction in venous capacitance, an increase in central pressures (particularly right atrial pressure), and an increase in cardiac output during administration of the levoisomer. We believe this may be delivered by the peripheral α agonistic mechanism. So, much of dobutamine's cardiac output may be via peripheral vascular manipulation.

Basically, I think the peripheral vascular effects probably are extremely important.

Dr. Gheorghiade: I think it depends on what type of patients we are looking at. In the acute myocardial infarction (MI) patient with high pulmonary artery wedge pressure and low cardiac output, for example, dobutamine therapy might temporarily increase cardiac performance at the expense of increased contractility of the stunned myocardium.[2] It is not known if this will preserve ventricular function in that area, particularly in patients in whom coronary flow is not restored.

We have seen that patients with long-standing severe congestive heart failure (CHF) who are admitted with exacerbation of symptoms may not respond to dobutamine, and this could be related to down-regulation of their cardiac β receptors. However, these patients are likely to respond to intravenous digoxin therapy.[3,4]

Dr. Leier: I agree, but I think the point you made about careful characterization of these patients becomes critical, since it is clear that acute heart failure is much different from decompensated chronic heart failure and that the types of acute heart failure also differ tremendously. The devastating acute myocarditis we have seen is much different from the acute MI.

I am interested in Dr. Mancia's thoughts about ibopamine. What is the experience in Italy and what are your impressions?

Dr. Mancia: It is clear that the positive inotropy of ibopamine referred to in early studies[5,6] has been overemphasized. The drug is largely a vasodilator, and the potential it may have compared with other vasodilators is that it can increase renal blood flow markedly.[7] So there may be an advantage to using ibopamine[8,9] in patients in whom renal function has been adversely affected by the angiotensin-converting enzyme (ACE) inhibitors.

There is evidence that norepinephrine levels are markedly reduced with ibopamine. Thus, the drug seems to belong to the group of those that can switch off sympathetic overactivity in CHF rather than with the classic vasodilators.

Dr. Leier: There may be some transient vasoconstriction with ibopamine in the first hour postdose, but after that it is a vasodilator in terms of hemodynamic criteria.

Dr. Lewis: Do you think that digoxin may enable β receptors that are down-regulated to become up-regulated by replacing one inotropic mechanism for another?

Dr. Leier: Yes, in terms of turning off endogenous sympathetic activity, plus not having to administer an exogenous β agonist.

Dr. Kelly: By far, endothelin is the most potent inotropic agent discovered so far. The foot of the dose–response curve in isolated papillary muscle preparations is in the picomolar range, and in isolated cells it is in the femtomolar range. It has a mechanism of action unlike most any other positively inotropic agent, and it induces about a 100% increase in contractility in both isolated papillary muscles and isolated cells. This clearly is a calcium sensitization phenomenon, similar to what we find with α-adrenergic agents such as phenylephrine.

Dr. Creager: Would you define calcium sensitization?

Dr. Kelly: It is usually defined in the context of the presence or the absence of the sarcolemma. One finds a shift to the left of the dose response relation of a positively inotropic agent at any given level of external or internal calcium activities, depending on the preparation.

Dr. Mancia: Is this calcium sensitization selective for the heart? If it were also produced in the peripheral circulation, would it not increase resistance in heart failure as well?

Dr. Leier: That is an interesting question. DPI 201–106, the calcium sensitizer, actually causes peripheral vasodilation, when it should sensitize the musculature to calcium. Nobody knows why this happens, but Hof and Hof[10] speculate that it may have some calcium antagonistic properties.

There is some question about endothelin in the intact animal. Dr. Greg Eaton (a research fellow working in the laboratories of Dr. Phillip Binkley and Robert J. Cody) infused endothelin into an anesthetized dog model and demonstrated an increase in pulmonary wedge pressure and systemic vascular resistance, and a reduction in stroke volume. It appeared that the reduction in stroke volume was greater than that attributable to the increase in afterload. It made us consider whether endothelin in the intact cardiovascular system may not have negative inotropic properties.

Dr. Kelly: Endothelin is, in reality, a cytokine. It is a locally released and locally consumed hormone. It cannot be used for purposes of positive inotropy, but it is, by a very unusual mechanism, a very potent positive inotropic agent.

Dr. Leier: The question is whether one can transfer the positive inotropic response seen in the isolated-cell or papillary-muscle preparation to the intact system.

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Recognition and Management of Asymptomatic Patients with Left Ventricular Dysfunction

David McCall, MD, PhD

In recent years there have been encouraging developments in the therapy for congestive heart failure. Vasodilator therapy, as an adjunct to digitalis and diuretics, has made a major impact. Vasodilator therapy results in improved left ventricular (LV) ejection fraction, improved functional capacity, and enhanced quality of life. When an angiotensin-converting enzyme (ACE) inhibitor is used, several studies published since 1988 show that these improvements are accompanied by improved survival. Yet many questions remain. Principal among these is how to approach the patient who has significantly depressed LV function, but is asymptomatic or has only minimal symptoms. In these patients the prognosis cannot be based on New York Heart Association (NYHA) functional class, but must reflect objective measurements of ventricular function. Any intervention should be specifically designed to improve survival, since functional capacity and quality of life are apparently unimpaired. On the other hand, there are no data at present to suggest that intervention in these patients will improve survival. This article considers the evaluation of such asymptomatic patients and potential therapeutic approaches. These are the use of cardiac glycosides, the use of ACE inhibitors, or their combination. Circumstantial evidence supporting their use in this select patient population is considered. It is stressed that any decision to intervene therapeutically in the asymptomatic patient must be made by the physician on an individual basis.

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When confronted with a patient who has symptoms of congestive heart failure (CHF) and severe left ventricular (LV) dysfunction, it is easy to set therapeutic targets. These targets should include improvements in systolic performance, functional capacity, hence the patient's quality of life, and, if possible, increased survival. Both digitalis[1] and vasodilator therapy[2] will produce significant improvements in the systolic performance of the failing left ventricle. Several drugs, especially vasodilators,[2] will considerably improve functional capacity. It was not until recently, however, that several large clinical studies[3–6] demonstrated that vasodilator therapy, specifically using angiotensin-converting enzyme (ACE) inhibitors,[4–6] could significantly improve survival in patients with CHF. These data, overall, suggest that the combination of digoxin, a diuretic, and an ACE inhibitor offers the best opportunity of achieving all 3 therapeutic goals.

For the asymptomatic or minimally symptomatic patient, the decisions are much more difficult. Therapeutic guidelines are few, since functional capacity cannot be used as a guide to, or as a measure of the success of, therapy. Since functional capacity is preserved, the only reason to treat the asymptomatic or minimally symptomatic patient is to improve survival. This could possibly be achieved by modulation of the deleterious neurohumoral mechanisms involved in heart failure, thereby preventing progression of LV dysfunction.

In general terms, survival in patients with heart failure can be predicted on the basis of New York Heart Association (NYHA) functional class. As recently as the Vasodilation–Heart Failure Trial (VHeFT) trial[3] and the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS) trial,[4] it has been shown that, with increasing functional class, there is an increasing mortality rate, with the 1-year mortality exceeding 50% in patients with NYHA functional class IV heart failure.[4] Obviously, such a guide cannot be used as

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an indication for therapy in the asymptomatic patient.

On the other hand, following a myocardial infarction, survival is closely related to ventricular function, as measured by the LV ejection fraction.[7] The same is true in patients with CHF.[8] Therefore, rather than basing treatment on NYHA functional class, perhaps the LV ejection fraction would be a better indicator for intervention.

It is common in clinical practice to estimate the severity of a patient's LV dysfunction by functional capacity, particularly functional capacity during exercise. However, there is a lack of correlation between exercise capacity and resting index of LV function.[9–13] In one study,[11] there was no apparent correlation between exercise duration and noninvasive indexes of ventricular performance carried out at rest. Another study evaluated ejection phase indexes of ventricular performance in light of treadmill exercise capacity.[10] The latter study indicated that normal or near normal exercise capacity could coexist with a severely depressed LV ejection fraction.[10] Although it has been traditional to do so, it is probably unwise to use functional capacity alone as a prognostic index. Clearly, some patients with markedly depressed LV function—which ultimately will determine prognosis—have normal or near normal exercise capacity.

Why do some patients with very poor LV function retain their ability to exercise? It is possible that, although there is a depressed LV stroke volume, cardiac output is maintained by a resting tachycardia and by an appropriate heart rate response to exercise. Stroke volume may be preserved by an increase in end-diastolic volume, which in turn may reflect favorable changes in LV compliance.[10] Further, upright exercise is associated with increases in LV volume.[14] This may augment cardiac output by the Frank-Starling mechanism. During exercise, there is a physiologic decrease in systemic vascular resistance, which will decrease afterload and may improve ventricular performance. Finally, some patients may develop microvascular changes in the pulmonary circulation that protect against adverse effects of high pulmonary venous pressures. This was demonstrated many years ago in patients with mitral stenosis.[15] Clearly, there are many reasons for the frequently seen disparity between functional capacity and measures of ventricular performance.

IDENTIFICATION OF PATIENTS

Which patients constitute the group with normal to near normal functional capacity and depressed LV function? Many have had a myocardial infarction and have not resumed their prior physical activities. Two recent studies[16,17] were specifically designed to evaluate the effect of therapy on asymptomatic patients after myocardial infarction. All of the patients showed evidence of depressed LV function but had no heart failure symptoms.

Following a myocardial infarction, many patients do not return to their preinfarct activity level. This may be due to overall anxiety or specific fear of provoking further chest pain. Because of this inactivity, they may not be aware of any functional limitation. Other patients may have consciously or subconsciously gradually decreased their exercise and functional activity. On questioning family members, however, it may become apparent that there has been marked restriction of activity in some of these patients, who frequently will show an impaired response to treadmill testing. Other patients, who have experienced gradual deterioration in LV function, may remain asymptomatic by developing one or more of the compensatory mechanisms described before. Finally, it must be remembered that many factors contribute to functional limitation in patients with heart failure.[18,19] For example, many patients are limited by fatigue[18] rather than dyspnea, and this can be correlated with changes in arterial pH and lactate levels. These latter changes[19] presumably reflect decreased aerobic, and increased anaerobic, metabolism in exercising skeletal muscle. Some patients, because of skeletal muscle conditioning, may develop less acidosis and lactate production and be less fatigued than others.

Many of these patients will be found at routine office visits following a myocardial infarction. On physical examination, there may be a third heart sound or a soft mitral regurgitation murmur. Chest radiograph may show an increased cardiothoracic ratio and perhaps some pulmonary vascular redistribution, and yet the patient may vigorously deny symptoms. Others will be seen at routine examinations, e.g., for life insurance, at which similar physical and radiologic findings may point to evidence of LV dysfunction. Something as simple as a routine chest radiograph, perhaps for a chronic cough, may bring such patients to the physician's attention. Finally, many of these patients may not present with the classic symptoms of CHF. Their complaints may be of general malaise and fatigue, and only a careful physical examination will show evidence of significant impairment of LV performance.

EVALUATION

Once the presence of LV dysfunction has been determined, the evaluation of the patient is no different from that of the symptomatic patient. All attempts should be made to define the etiology of the LV dysfunction.[20] In particular, a careful search should be made for any remediable causes, since correcting all underlying causes offers the best chance for improved survival.[20] A careful history may point to evidence of repeated ischemic episodes, or a remote history of a viral myocarditis. Physical examination, in addition to evaluating the patient's overall cardiac status, should pay particular attention to the possibility of surgically correctable lesions such as congenital heart defects or rheumatic heart disease. An electrocardiogram may show an old myocardial infarction or the presence of LV hypertrophy, the latter suggesting a history of hypertension. Many of the electrocardiographic changes, however, will be rather nonspecific and would be unlikely, per se, to lead to a specific diagnosis. A chest radiograph should be obtained to evaluate heart size and the presence or absence of pulmonary vascular congestion.

A good quality 2-dimensional Doppler echocardiogram will more accurately define the degree of LV dysfunction. It will also evaluate the severity of any valvular disease and the presence of atrioventricular valve regurgitation. The echocardiogram may reveal segmental wall motion abnormalities pointing to an ischemic etiology or there may be concentric LV hypertrophy. In the absence of other pressure overload conditions, this would point to long-standing hypertension as an etiologic consideration. Finally, many of these patients should undergo cardiac catheterization with selective coronary arteriography. The group at the University of California, Los Angeles, has shown that many patients with impaired LV performance, on the basis of chronic ischemic heart disease, may benefit from coronary artery bypass surgery and revascularization.[21] In short, no effort should be spared to define potentially reversible causes of poor ventricular performance.

It is debatable whether some measurement of functional capacity should be made. Certainly, for the patient who is truly asymptomatic with preserved exercise capacity, this will serve no meaningful purpose. It would not even serve as a measure of the efficacy of therapy. Exercise testing, with or without respiratory gas exchange,[22] to define the anaerobic threshold would serve to identify those patients who are not truly asymptomatic, but who are considered asymptomatic because they have decreased their activity level. This can be carried out using a standard Bruce or Naughton exercise protocol or, more simply, measuring how far the patient can walk in a 6-minute walk test.[23] Unfortunately, tests of functional capacity are notoriously nonreproducible and, other than determining whether the patient is asymptomatic, it is unlikely that exercise testing will perform any useful function in this select subgroup of patients.

TREATMENT

Having identified and evaluated the asymptomatic patient with significant LV dysfunction, the question remains whether or not to treat. Since the patient is asymptomatic, there can be no symptomatic benefit from treatment. Little or no improvement in functional capacity or quality of life will be appreciated. Treatment, therefore, must be directed toward improving ventricular function. The rationale is that improvement in ventricular function should be long-term and treatment should slow the disease progression. It must be pointed out that even in patients with NYHA class I heart failure, mortality is high. Recently, in a group of patients classified as NYHA class I and receiving hydralazine and isosorbide dinitrate, the annual mortality rate was 14.9%.[6] Therefore, in addition to a direct effect on ventricular performance, treatment would require some modulation of the neurohumoral mechanisms[24] involved in heart failure. The therapy should address both the circulating and tissue[25] neurohumoral mechanisms, which probably account for the progression of LV dysfunction and the patient's ultimate death. This is true in both asymptomatic and symptomatic patients. It has been clearly shown that, in patients with depressed LV function, even though asymptomatic, there is activation of various neuroendocrine pathways[26] (Figure 1).

The premise is that by improving ventricular function, modulating neurohumoral mechanisms, and slowing disease progression, survival will be improved. Although no data are available to substantiate this premise, it is hoped that the answer will be forthcoming when the results of the second, prevention component of the Studies of Left Ventricular Dysfunction (SOLVD) are published.[26] This arm of the study will specifically evaluate the effect of enalapril treatment in asymptomatic, or minimally symptomatic, patients, whose LV ejection fraction is $<35\%$.

The therapies available to achieve the above goals include inotropic support, diuretics, and nitrates and vasodilators. The effect of diuretics is largely to decrease circulating volume and decrease ventricular preload. As such, they are most useful in treating the patient who has symptoms of pulmonary congestion. Their use in an asymptomatic patient is questionable. The same is true of nitrate therapy. Nitrates primarily act as venodilators, decreasing venous return and decreasing LV and right ventricular filling pressures. They have only a minimal effect as arterial dilators and as afterload-reducing agents. For these reasons, any real benefit from nitrate therapy is unlikely. Their use in CHF is largely directed toward symptomatic improvement in the patient with congestive symptomatology.

Digitalis: Digitalis preparations have been in use for >200 years and at this time remain the only class of positive inotropic agents approved by the U.S. Food and Drug Administration for long-term oral use. In the past decade, many new positive inotropic agents, including those with catecholamine-mediated effects, and phosphodiesterase inhibitors have been developed. None of these has been shown to be superior to digoxin[27] in improving function. Some studies have even suggested that they may be associated with increased mortality in patients with CHF.[27,28] Because of this, none of these agents has received Food and Drug Administration approval for long-term use. Certainly, their use in the asymptomatic patient with ventricular dysfunction could not be recommended.

Few clinicians would question the fact that digoxin, when administered acutely, has a positive inotropic effect on the failing myocardium. The real debate, in the last few years, is whether improvement in systolic performance is maintained with long-term therapy. Some studies[29,30] have shown that, in patients with CHF who are in sinus rhythm, digoxin appears to have little or no benefit. This is based on findings that there may be no sustained positive inotropic effect.[31] Other studies[30] have shown no deterioration in noninvasive indexes of LV performance after digoxin withdrawal. Others[32] have questioned this. There is evidence of marked deterioration in invasively measured parameters of cardiac function[33] and in clinical status[34] after digoxin is withdrawn. Arnold et al[33] found that withdrawal of digoxin was almost universally associated with a decrease in stroke

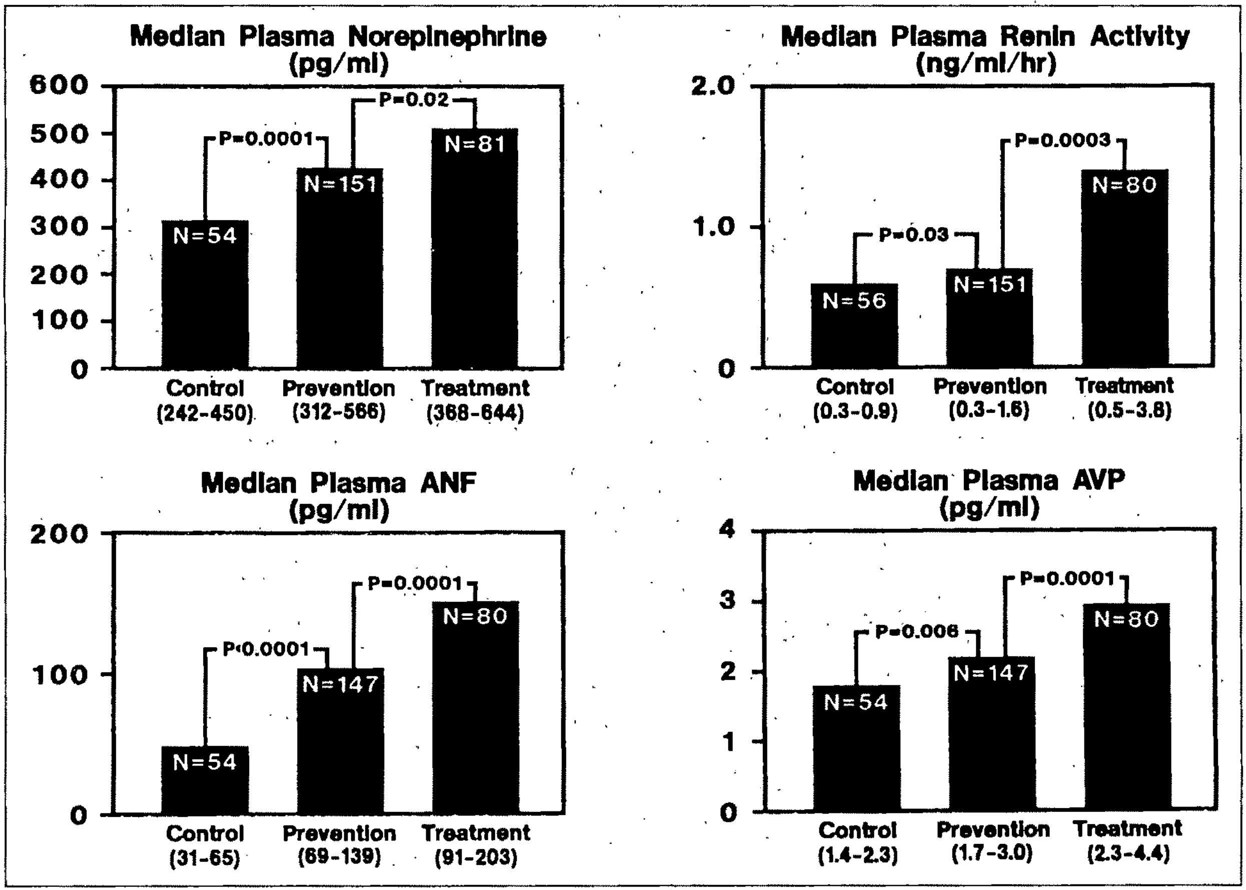

FIGURE 1. Increases in neuroendocrine activity in the prevention and treatment patients in the Studies of Left Ventricular Dysfunction (SOLVD) trial. Prevention patients are the asymptomatic group with depressed left ventricular function. ANF = atrial natriuretic factor; AVP = arginine vasopressin. (Reprinted with permission from *Circulation*.[26])

work index and an increase in pulmonary capillary wedge pressure. When these same patients were again given digoxin,[33] the hemodynamic parameters improved (Figure 2).

A more recent multicenter randomized trial compared the effects of captopril and digoxin in patients with NYHA class II–III CHF.[35] The patients were all in sinus rhythm and were randomized to receive either digoxin or captopril. In those receiving digoxin there was a significant increase in LV ejection fraction which was sustained throughout the study[35] (Figure 3). There was no significant increase in LV ejection fraction in the captopril-treated patients and the improvement in LV ejection fraction seen with digoxin was not associated with increased exercise time. Captopril did, however, significantly increase exercise time and, therefore, functional capacity, without a concomitant increase in LV ejection fraction.

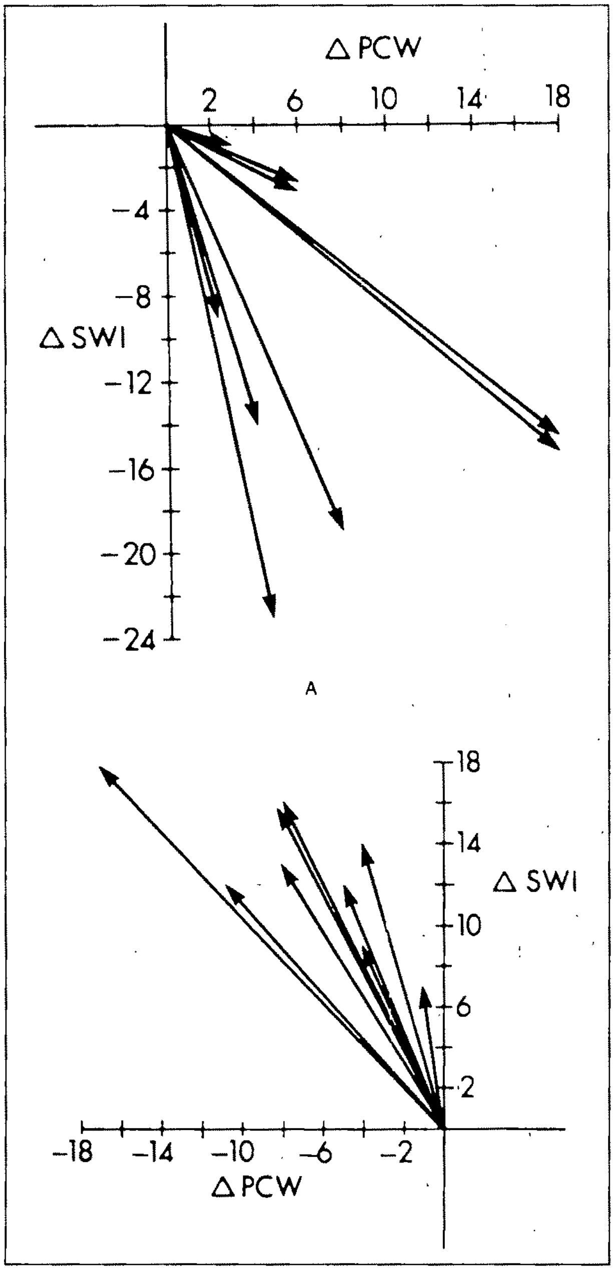

FIGURE 2. ***Top,*** **increases in pulmonary capillary wedge (PCW) pressures and decreases in stroke work index (SWI) in individual patients upon discontinuation of digoxin.** ***Bottom,*** **changes in PCW and SWI with acute readministration of digoxin. (Reprinted with permission from** ***N Engl J Med.***[33]**)**

Numerous other studies have shown a beneficial effect of digoxin therapy in CHF patients with sinus rhythm. A meta-analysis of these studies[32] showed that the odds ratio (Figure 4) for deterioration of heart failure in patients taking digoxin compared with those taking placebo was 0.28 (95% confidence intervals, 0.16–0.49). There is, therefore, good evidence that digoxin plays a beneficial role in improving ventricular performance and maintaining that improvement in patients with CHF.

Digoxin therapy would achieve one of the therapeutic goals, namely, improvement in ventricular function. Pooled data would also suggest[32] that long-term digoxin therapy significantly decreases the progression of dysfunction, if one uses worsening heart failure as a measure. Recently, cardiac glycosides were shown to modulate neurohumoral responses in heart failure.[36] Ferguson et al[36] demonstrated that, acutely administered, a cardiac glycoside decreased muscle sympathetic nerve activity and forearm vascular resistance in patients with heart failure. This effect was not seen in normal control subjects[36] and reflects a sympatholytic drug effect, independent of the effect on ventricular function. Long-term digoxin therapy also decreases circulating norepinephrine[37] and renin[38] levels. Therefore, digoxin not only improves ventricular performance, but also produces some modulation of the neurohumoral aspects of CHF. Clearly, then, digoxin has a beneficial role in the management of CHF.[1] Although this role has been downplayed with the advent of vasodilator agents, it should be remembered that in all trials of vasodilators they were given as adjunctive therapy to patients already receiving digoxin and diuretics.

No data show that digoxin therapy improves survival in patients with CHF. Indeed, because of its known toxicity,[1] digoxin therapy could perhaps be associated with decreased survival, particularly in patients with ischemic heart disease. This concept of excess mortality with digoxin therapy stems largely from 2 reports[39,40] in which there appeared to be a higher mortality in patients taking digoxin following a myocardial infarction. Subsequent studies[35,41] have not confirmed this finding. There does not appear to be an excess mortality associated with digoxin therapy.[1] Indeed, in a captopril-digoxin trial,[35] there was no excess mortality in the digoxin-treated group. A multicenter trial,[27] comparing oral milrinone with digoxin and placebo, showed that mortality in the digoxin-treated patients was no greater than that in the placebo group. The same was not true of the milrinone group, where there appeared to be a trend toward excess mortality.

If improvement in ejection fraction is associated with a decrease in mortality, as is suggested by the Veterans Administration cooperative heart failure trial,[3] then it might be reasonable to consider digoxin even in the asymptomatic patient. Unfortunately, few data support this contention. In one study, ouabain was given to asymptomatic patients with depressed LV function following a myocardial infarction.[42] The drug caused a significant decrease in LV end-diastolic pressure and an increase in LV stroke work index.[42] A further study by DeMots et al[43] assessed ouabain's effect in asymptomatic patients with severe coronary artery disease. They were able to demonstrate a decrease in LV end-diastolic and end-systolic volume indexes.[43] These studies provide little direct support for the use of digoxin in the asymptomatic patient. Intuitively, however, it would seem that improvement in ventricular performance and modulation of neurohumoral mechanisms may have a beneficial or, at least, temporizing effect on the progression of LV dysfunction.

Vasodilator therapy: In the 1970s considerable interest developed in using vasodilators to treat patients with heart failure.[2] The rationale was to decrease the high systemic vascular resistance, mediated by the high α sympathetic tone, and

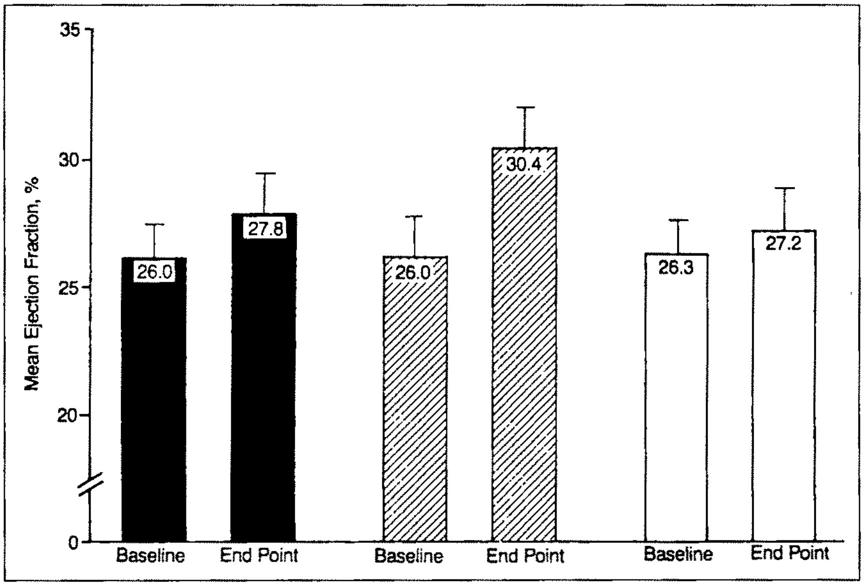

FIGURE 3. Left ventricular ejection fraction at baseline and after 6 months' treatment with captopril (*solid bars*), digoxin (slashed bars), and placebo (*open bars*). (Reprinted with permission from *JAMA*.[35])

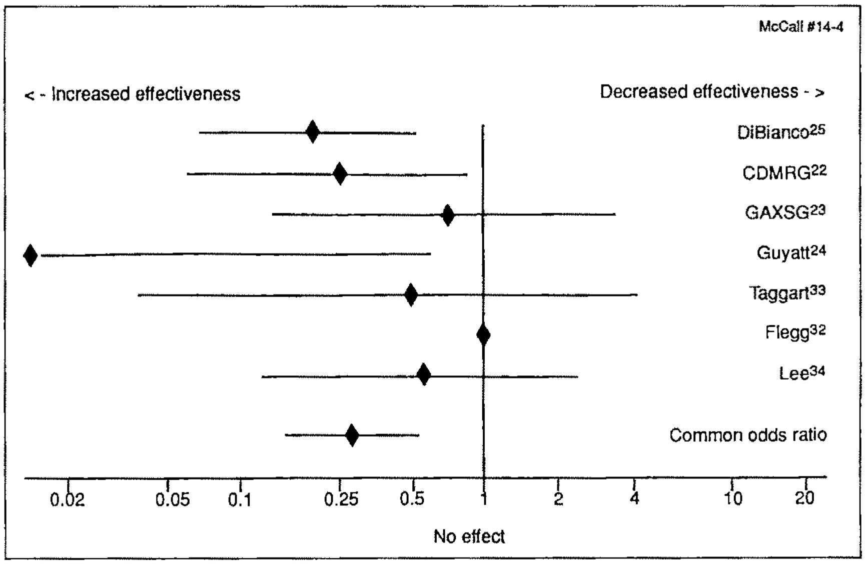

FIGURE 4. Meta-analysis of digoxin versus placebo in various trials in heart failure patients. The data show the odds ratio, with 95% confidence intervals, for withdrawal from the trial because of worsening congestive heart failure for patients randomized to receive digoxin or placebo. (Reprinted from *Am J Med*.[32])

thereby decrease the impedance to LV ejection.[2] This approach would increase cardiac output, improve tissue perfusion, decrease pulmonary congestion, and improve functional capacity. A wide variety of vasodilator agents were used[2] and numerous studies conclusively demonstrated that vasodilator therapy achieved, to some extent, its therapeutic goals. The decrease in systemic vascular resistance was associated with improved LV ejection fraction and cardiac output. Pulmonary pressures fell, pulmonary congestion was diminished, and the patient was symptomatically improved.[2] Functional capacity likewise increased. The excitement about vasodilator therapy grew with the 1986 publication of results of the Veterans Administration cooperative trial of vasodilator therapy in patients with functional class II–III heart failure.[3] In this trial, patients with heart failure, already receiving digoxin and diuretic therapy, were randomized to receive either placebo, prazosin, or a combination of hydralazine and isosorbide dinitrate. Mortality was decreased[3] in the patients receiving the hydralazine and isosorbide dinitrate combination, an effect that was not seen with prazosin. Although the mortality reduction with hydralazine and isosorbide dinitrate was small, it was statistically significant and represented the first evidence that this therapeutic approach could improve survival in heart failure patients.

The following year, the CONSENSUS Trial[4] demonstrated that adjunctive therapy with the ACE inhibitor enalapril caused a significant decrease in 1-year mortality in patients with NYHA functional class IV symptoms. In this study, the placebo group had a 52% mortality at the end of 1 year, in keeping with previously published mortality data for class IV heart failure patients. The enalapril-treated group, however, had only a 36% mortality at 1 year, a highly significant ($p < 0.001$) 31% reduction in relative risk. Subsequently, a much shorter (3 month) trial[44] of captopril compared with placebo was carried out in patients who largely had NYHA functional class II–III symptoms. With captopril therapy, at the end of 90 days there was a 4% mortality,[44] compared with 21% in a placebo group ($p < 0.01$). Once again, this trial was carried out in patients who were already receiving optimal therapy with digoxin and diuretics.

More recently, in 2 large multicenter trials,[5,6] patients who had NYHA functional class II–III heart failure were shown to benefit, in terms of mortality, from adjunctive therapy with enalapril. In one of these trials, the second Veterans Administration cooperative heart failure trial,[6] enalapril was shown to be superior to the combination of hydralazine and isosorbide dinitrate in terms of mortality. After 2 years, there were significantly fewer deaths in the enalapril group (18%) than in the hydralazine–isosorbide dinitrate group (25%) ($p = 0.016$). This represented a 28% reduction in mortality. The SOLVD trial[5] enrolled almost 2,600 patients with NYHA functional class II–III heart failure. The mortality rate was 39.7% in the placebo group and 35.2% ($p = 0.0036$) in the enalapril-treated group[5] (Figure 5). In this study, as in the CONSENSUS trial,[4] the major effect on mortality was seen in those deaths attributed to progressive heart failure.

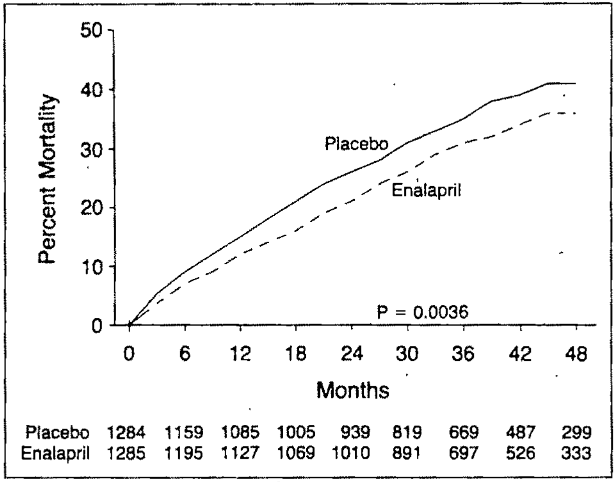

FIGURE 5. Mortality curves for patients with New York Heart Association class II–III heart failure randomized to receive placebo or enalapril. The numbers of patients alive in each group at the end of each period are shown at the bottom. (Reprinted with permission from *N Engl J Med*.[5])

ACE inhibitors have lived up to their early promise. Early studies showed significant improvements in hemodynamic indexes,[2] functional capacity, and quality of life. Several studies[4–6,44] have now demonstrated that they improve survival. Their effect is more than that of simple vasodilation and it probably relates to their ability to modulate favorably the neurohumoral components of heart failure, both at a circulating[24] and a tissue[25] level. The ACE inhibitors have become the drugs of choice for vasodilator therapy in heart failure. In addition, they do not show hemodynamic tolerance, a feature of long-term nitrate therapy, and have a favorable dosing interval and a very acceptable side-effect profile.

All of the studies discussed herein have been carried out in moderately to severely symptomatic patients. As is the case with digoxin, there are few data regarding the value of ACE inhibitors in asymptomatic patients. Two studies published in 1988[16,17] evaluated the effect of treatment with the ACE inhibitor captopril in asymptomatic patients with depressed LV function following a myocardial infarction. In one,[17] 59 patients with LV ejection fraction of $\leq 45\%$ were randomized to receive captopril or placebo, 11–31 days after infarction. Repeat cardiac catheterization was performed after 1 year for hemodynamic assessment. Several of the patients were evaluated with exercise treadmill tests every 3 months. At the end of 1 year, there was virtually no ventricular dilation in the captopril-treated group, but the end-diastolic volume increased by 21 mL in the placebo group (Figure 6). LV filling pressure remained elevated with placebo therapy, but decreased with captopril, and the patients given captopril had significantly increased exercise capacity. In another study,[16] 60 patients with LV ejection fractions $<45\%$ were randomly assigned to receive captopril, furosemide, or placebo. LV volumes and hemodynamic indexes were measured at 1, 3, 6, 9, and 12 months of follow-up. As in the other study, the placebo and furosemide groups showed significant increases in ventricular volumes. These were unchanged or slightly reduced in the captopril group. The captopril group also showed significant increases in stroke volume index and ejection fraction.[16] The beneficial changes in the captopril group were significantly different from those in the others. Neither of the studies reported mortality data during the brief 1-year follow-up. It would appear that, in these highly selected asymptomatic patients, the ACE inhibitor captopril had a beneficial effect on LV dynamics, prevented progressive dysfunction, and improved functional capacity. In these studies,[16,17] in contrast to the other studies with ACE inhibitors, the beneficial effect of the ACE inhibitor was seen in patients who were not already receiving digoxin therapy.

CONCLUSION

Both digoxin and ACE inhibitor therapy are associated with improved LV function and modulation of the deleterious neurohumoral mechanisms in heart failure. In addition, with ACE inhibitors, but not with digoxin, there appears to be improved survival in the symptomatic patients studied. It is worth remembering, however, that in all of these studies, with the exception of 2,[16,17] the ACE inhibitor was adjunctive to standard therapy with digoxin and diuretics. It is possible that the beneficial effects accrued from the combined administration of these 3 agents. Whether this combination would result in improved survival of asymptomatic patients with depressed LV function is unknown at this time. To decide to treat these patients is to commit them to long-term therapy, possibly with 2 drugs. Although intuitively appealing, data are insufficient to justify the use of ACE inhibitors in these patients as yet.

Despite this, others[45] have stated strongly that all patients with LV dysfunction should be treated with ACE inhibitors. If this is the case, then why

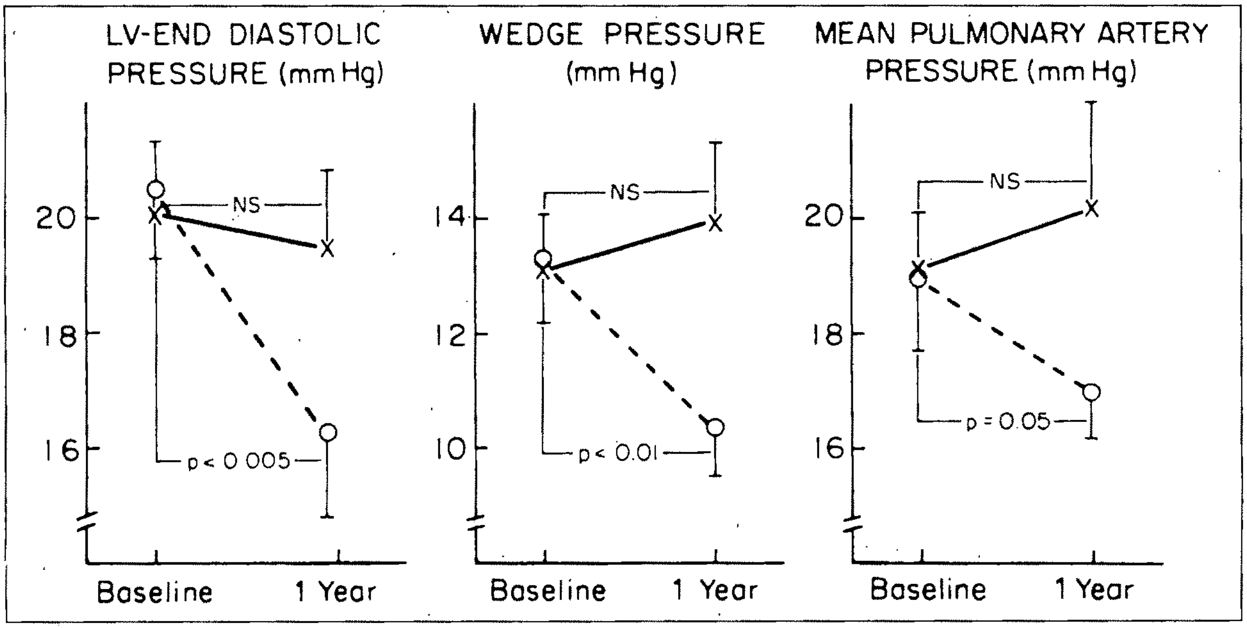

FIGURE 6. Changes in left ventricular (LV) end-diastolic pressure, wedge pressure, and pulmonary artery pressure from baseline to 1 year in patients randomized to receive placebo (x—x) or captopril (o---o). (Reprinted with permission from *N Engl J Med*.[17])

not also treat with digoxin? After all, digoxin produced greater increases in LV ejection fraction than captopril.[35] Further, all studies showing the benefit of ACE inhibitors were carried out in patients who were already taking digoxin. A combined effect cannot be excluded and if therapy is considered, then consideration must be given to the combination. There are still many unanswered questions and the physician must decide the merits of medicating the asymptomatic patient on an individual basis. That the risk–benefit ratio with either drug alone or with the combination is low provides some comfort.

To some extent this question may be answered in the next few months, with the publication of results of the second component of the SOLVD trial. This prevention arm will evaluate the effect of enalapril on survival in asymptomatic patients whose LV ejection fraction is <35%. It will be an important study and will largely resolve our present dilemma: whether or not to treat the asymptomatic patient with severely depressed LV function.

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DISCUSSION

Dr. Yusuf: In the Studies of Left Ventricular Dysfunction (SOLVD), we screened all patients with an ejection fraction (EF) <35%, and found that for every patient with asymptomatic low EF there were 2–2.5 patients with symptomatic heart failure. So I think it is difficult to characterize the asymptomatic patient with a low EF. "Asymptomatic" in SOLVD is defined as a patient who does not need digoxin, diuretics, or vasodilators for heart failure.

EF, however, has proven to be the most powerful predictor of mortality in SOLVD. The second most powerful is New York Heart Association (NYHA) classification, which is enormously significant. Age is important, as is cardiomegaly and the 6-minute walk test. Etiology is not very important. So I think we may say that some of the simple tests predict mortality accurately.

Dr. Francis, in discussing the Vasodilator–Heart Failure II Trial (V-HeFT II), you said there was an increase in plasma norepinephrine levels with hydralazine and isosorbide dinitrate that was not seen with enalapril. Is that correct?

Dr. Francis: On balance, it appears that the V-HeFT II data are consistent with those of other studies, which show that there may be a temporary (6 months to 1 year) blocking of the sympathetic nervous system with enalapril. It is not very substantial, but it is statistically significant when compared with hydralazine and isosorbide dinitrate.

Dr. Yusuf: Could you say that hydralazine causes reflex sympathetic activation?

Dr. Francis: That is true in normal subjects, but the more advanced the heart failure, the less reflex activation there is. This is a complex issue. In very sick patients, we do not see much reflex tachycardia with hydralazine.

Dr. Leier: A late colleague, Donald Unverferth, was convinced that there was no such thing as asymptomatic left ventricular (LV) dysfunction. When we took the histories of a number of "asymptomatic" patients, we found that those patients who had quit a physical activity allegedly because of age or lack of conditioning may have, in fact, developed symptoms of LV dysfunction. When we put these patients on the treadmill, they did not have the oxygen uptake of age-matched control subjects. I wonder whether "asymptomatic" patients with cardiomegaly who are hospitalized for a workup should be treated and no longer considered asymptomatic.

Dr. McCall: If somebody has cardiomegaly, I think they have a symptom, or evidence, of LV dysfunction. This is like talking about the "asymptomatic" postinfarct patient. That person is not asymptomatic; he or she has had a major symptom of coronary disease.

Dr. Yusuf: Obviously, an angiotensin-converting enzyme (ACE) inhibitor will improve the condition of a patient with congestive heart failure. However, we found mortality rates for SOLVD prevention trial class I patients were substantially lower than those for SOLVD treatment trial class I patients.

Dr. Gheorghiade: NYHA functional class I implies mild heart failure. However, this is not always the case, since many class I patients have severe LV dysfunction and very abnormal rest and exercise hemodynamics.[1–4] In addition, the mortality or the development of clinical CHF for this group with severe but asymptomatic LV dysfunction may be as high as 20–30% at 1 year of follow-up. The severity of heart failure is sometimes difficult to assess, since there is a poor correlation between symptoms,[1] physical,[2,3] and chest radiographic findings and central hemodynamics and LVEF.[4]

Dr. Lewis: I have always conceived that the relatively asymptomatic heart failure patient is someone whose peripheral vascular mechanism has adapted to the limited output. Dr. McCall, how do you feel about this?

Dr. McCall: No data have substantiated that. I think there are patients who adapt to low blood flow, but I do not know what the adaptive mechanisms are.

Dr. Cody: I think that treatment of asymptomatic patients should hinge on whether we can either prevent myocardial remodeling and the resultant cardiomegaly, or delay the onset of cardiomegaly.

In the 1990s, the focus may be on this approach, rather than the traditional approach of reasoning backward from functional class IV failure to the asymptomatic patient.

Dr. Yusuf: The SOLVD prevention trial will provide us with data on mortality, morbidity, development of clinical heart failure, and hospitalization for patients with asymptomatic LV dysfunction. In addition, various substudies will provide detailed information on physiologic parameters. We will then obtain a complete picture both on the clinical outcomes and physiologic parameters in asymptomatic patients.

Dr. McCall: The longitudinal natural history of these patients is also going to be an important determinant of whether we should intervene.

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Management of Refractory Congestive Heart Failure

Robert J. Cody, MD

Despite recent advances in the treatment of congestive heart failure (CHF), many patients continue to present with symptoms refractory to digoxin, diuretic, and vasodilatory therapy. Since it is unlikely that this population will decrease in the near future, practical approaches to management of refractory CHF are reviewed. Refractory CHF here is defined as New York Heart Association (NYHA) functional class III–IV heart failure, despite maximal drug therapy. Before such a diagnosis is made, the patient should be treated with digoxin, diuretics, and a vasodilator. Approach to therapy requires assessment of changing clinical status and pathophysiology, optimizing oral drug treatment, and providing temporary parenteral support when indicated. Specific attention should be given to factors that influence the optimal response to each of these 3 treatment classes. A theoretical, but unproven, concept suggests that combined vasodilatory therapy may be appropriate as long as excessive hypotension is avoided. In the course of management, a decision is required as to whether further optimizaion of therapy can be achieved on an outpatient basis. Hospital-based intravenous inotropic support given for 2–4 days will often provide the opportunity to restructure patient therapy.

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With much current interest in the management of mild congestive heart failure (CHF) and asymptomatic left ventricular (LV) dysfunction,[1,2] it is important to consider the other end of the spectrum, namely, the management of refractory CHF. The patient with refractory CHF presents a major therapeutic challenge, whether encountered in the outpatient setting or referral center. The purpose of this article is to define refractory CHF and to outline pragmatic approaches to management. It is unlikely that this population will decrease in the 1990s. In fact, it is conceivable that the CHF population will increase.[3] A considerable number of patients who previously may have died following a myocardial infarction are today undergoing angioplasty or receiving thrombolytic therapy that often yields a dramatic favorable outcome. These modalities can limit the size of myocardial infarction and also reduce patient mortality; however, the remaining myocardial damage may still progress to CHF. Furthermore, the increasing elderly population in the United States, which comprised >10% of the total population in 1984,[4] will likely produce a concomitant increase in the incidence and complexity of heart failure.

DEFINITION AND BASELINE MANAGEMENT

For the purposes of this presentation, refractory CHF is defined as patients with New York Heart Association (NYHA) functional class III–IV heart failure, in whom symptoms have not improved, or have actually worsened, following recent attempts to escalate therapy. Typically, this patient population is likely to evidence substantial fluid retention and/or significantly reduced cardiac output ("low-flow state"). Treatment with digoxin, diuretics, and a vasodilator regimen should have been attempted prior to diagnosis; otherwise, it would not be reasonable to consider the CHF refractory.

Even though several multicenter studies[2,5,6] have reported favorable outcomes with combined digoxin, diuretic, and vasodilator therapy, the question may be asked: Can patients treated in this

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manner still present with cardiac decompensation? The answer, in fact, is revealed in these same studies. In the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS),[6] for instance, many patients already receiving digoxin, diuretics, and a vasodilatory still had functional class IV failure. Despite the superiority of the combined regimen of digoxin, diuretics, and the angiotensin-converting enzyme (ACE) inhibitor enalapril over placebo in this study, the 1-year mortality rate among enalapril-treated patients approximated 40%. In the Prospective Randomized Milrinone Survival Evaluation (PROMISE) trial of milrinone,[7] entry criteria included evidence of recent functional class IV symptoms despite receiving digoxin, diuretic, and ACE-inhibitor therapy. More than 1,000 patients were enrolled. Similar observations can be drawn from the Vasodilator Heart Failure Trial II (V-HeFT II)[5] and Studies of Left Ventricular Dysfunction (SOLVD).[2]

Against this background, the approach to the patient with refractory CHF consists of 3 major factors: assessment of changing clinical status and pathophysiology, optimizing oral drug therapy, and providing temporary parenteral support when indicated.

CHANGING CLINICAL STATUS AND PATHOPHYSIOLOGY

In a patient with CHF who previously was well maintained on oral therapy, the appearance of refractory CHF should immediately raise questions regarding changes in clinical status and pathophysiology. Several factors influencing these changes are given in Table I.

TABLE I Factors Altering Clinical Status and Pathophysiology of Refractory Congestive Heart Failure

- New myocardial ischemia/infarction
- New or progressive myocardial mechanical defect (e.g., mitral regurgitation)
- Inadequately controlled hypertension
- Diabetes (particularly insulin-dependent)
- Dietary sodium indiscretion
- Progressive renal failure
- Coexistent disease processes (e.g., pulmonary)
- Patient-related drug therapy issues

The first major factor is ongoing myocardial ischemia or infarction. In the United States, coronary artery disease is the major cause of CHF. Once a patient has experienced multiple myocardial infarctions or one large myocardial infarction, subsequent progression to CHF may change the focus of patient management to the extent that the importance of ongoing ischemia due to coronary artery disease can be overlooked. Even in the absence of clinically overt ischemia such as chest pain or new electrocardiographic changes, ongoing ischemia, particularly at the endocardial level, may result in progressive ventricular dysfunction and dilation. A new myocardial infarction, of course, would have self-evident consequences.

More subtle, however, is the occurrence of ongoing ischemia that may compromise ventricular function. On a chronic basis, this could result in reduced LV systolic performance and diastolic dysfunction. Occurring more abruptly, it may cause complete cardiac decompensation and pulmonary edema.

A new or progressive cardiac mechanical defect, most commonly mitral regurgitation, can often be masked on cardiac examination; the severity of mitral regurgitation is not necessarily reflected in the cardiac murmur. Therefore, it can function as an independent variable, modulating the extent to which CHF is expressed. Despite the large number of published studies focusing on CHF, few have been able to assess fully the direct impact of mitral regurgitation on ventricular function.[8,9] Although clinical experience suggests that significant mitral regurgitation in essence provides a low-pressure escape for the failing ventricle, its long-term presence results in progressive dilation and worsening function of the ventricle, which is manifested symptomatically by pulmonary congestion and low cardiac output.

Like myocardial ischemia, the presence of hypertension may lose its importance once the patient has developed functional class III or IV heart failure. If a patient has a history of hypertension that is no longer present, one might argue that this is not a cause for concern. However, if the patient continues to have a systolic blood pressure in the 130–180 mm Hg range, or a diastolic blood pressure in the 85–100 mm Hg range, one could argue that additional blood pressure control is necessary. Both severe hypertension and severe CHF are accompanied by comparable increases in systemic vascular resistance (Figure 1). The major hemodynamic difference is the status of ventricular function and cardiac output. However, when hypertension progresses to where severe systolic dysfunction occurs, or if it is superimposed on CHF of another etiology, both the LV dysfunction and excessive LV wall stress due to the combination of these vascular disorders require particular attention. Even as the ventricle fails to the point where elevated systolic blood pressure is not generated (despite increased diastolic blood pressure), the long-standing hyper-

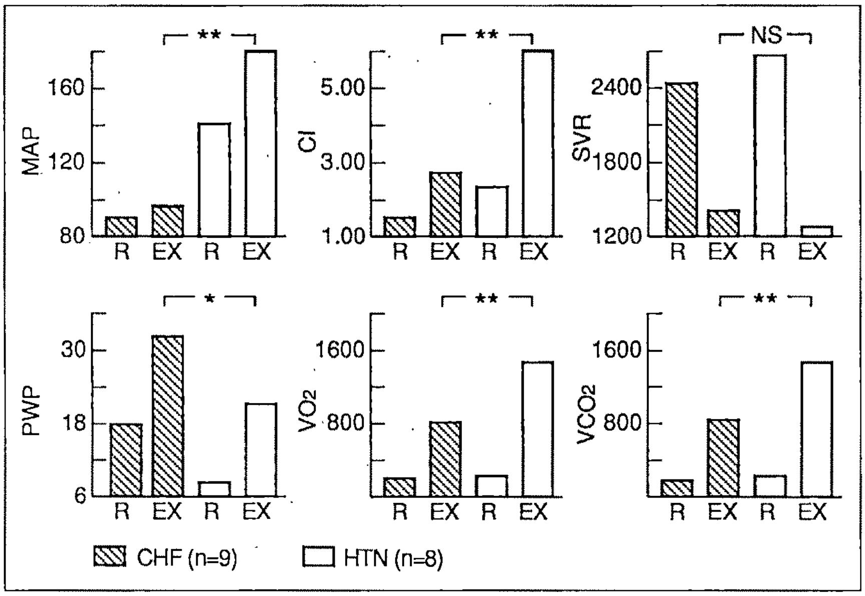

FIGURE 1. Comparative hemodynamic characteristics of patients with moderate to severe hypertension (HTN) and NYHA functional class III or IV congestive heart failure (CHF). Mean values are given, as is statistical significance, comparing peak exercise responses. In the HTN group, whereas mean arterial pressure (MAP, mm Hg) was much higher than in the CHF group, cardiac performance, as judged by cardiac index (CI, liters/min/m^2), pulmonary wedge pressure (PWP, mm Hg), oxygen consumption (VO$_2$, mL/min^2) and carbon dioxide production (VCO$_2$, mL/min), was maintained, despite comparable systemic vascular resistance (SVR, dynes/s/cm^5). R = resting; EX = exercise; NS = not significant. *$p < 0.01$; **$p < 0.05$.

tension does not suddenly disappear. In this regard, continued attention to blood pressure regulation is important.

Of course, diabetes remains an additional major factor in progressive ventricular dysfunction and worsening of CHF. Typically, diabetes is considered a cause of LV dysfunction, rather than a factor that may contribute to intermittent LV dysfunction. This concept, however, may be revised within the next few years, based on accumulating evidence citing hyperinsulinemia as a persistent vascular insult.[10] Both uncontrolled diabetes and perhaps even the adverse effects of chronic high-dose insulin use may soon be considered risk factors.

Dietary sodium indiscretion is an issue that continues to require attention. Patients with CHF frequently receive large doses of diuretics but, as described below, this does not obviate the need for ongoing dietary sodium management. Sodium intake is difficult to counsel and monitor. There are no firm guidelines regarding absolute sodium intake, but it would certainly be prudent to maintain sodium intake in the moderate range of 2–3 g.

Progressive renal failure can also alter clinical status and pathophysiology. Although many CHF patients typically have a serum creatinine level in the range of 1–1.5 mg/dL, which already reflects renal impairment (Figure 2), further progression to the range of 2.0–2.5 mg/dL induces a further, substantial reduction in renal function. This is particularly true in the elderly patient with CHF,[11] defined as >65 years of age. In the heart failure population, renal dysfunction continues to be prevalent among the elderly, even when all other aspects of heart failure are equal.

Attention must also be given to intermittent, coexistent disease, particularly pulmonary function abnormalities or pulmonary disease. Pulmonary embolus, even to the periphery of the parenchyma, may produce marked cardiac decompensation. Chronic lung disease is not unusual in the heart

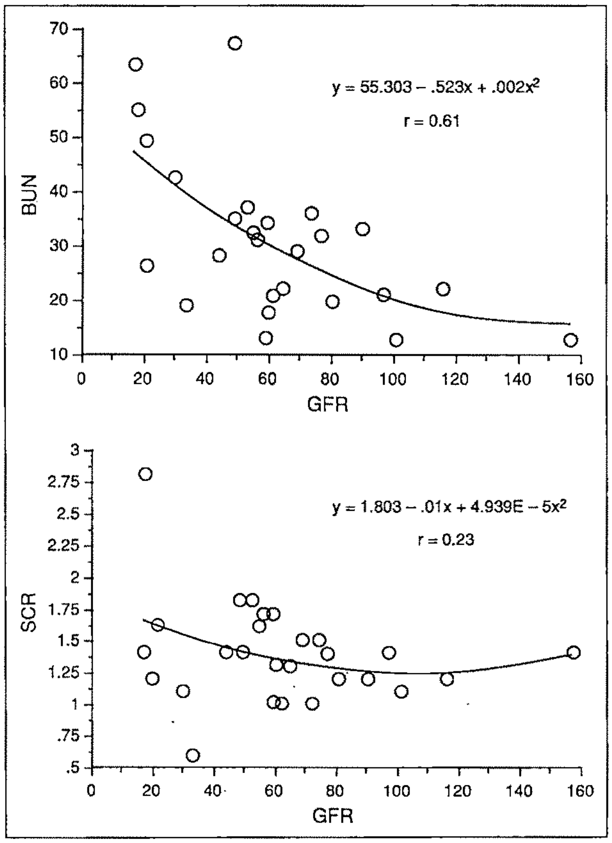

FIGURE 2. Relation of blood urea nitrogen (BUN, mg/dL) and serum creatinine (SCR, mg/dL) to glomerular filtration rate (GFR, mL/min), as determined by inulin clearance. Note that GFR may be substantially reduced even in patients with relatively normal BUN and SCR.

failure patient and is generally very difficult to differentiate from progressive heart failure. This is best done by the physician who follows the patient on a long-term basis. Pneumonia and other pulmonary and upper respiratory tract infections may also induce severe cardiac decompensation.

Finally, patient-related drug therapy issues must be considered. Noncompliance with therapy is always a factor. In symptomatic heart failure patients, however, this may be less so than in hypertensive patients, where the perception of illness is less apparent. Treatment of heart failure requires using multiple drugs throughout the day. The patient may misunderstand the drug regimen and inadvertently alter therapy. In the elderly patient, confusion, memory deficit, and other central neurologic disorders may compromise the ability to comply with therapy.

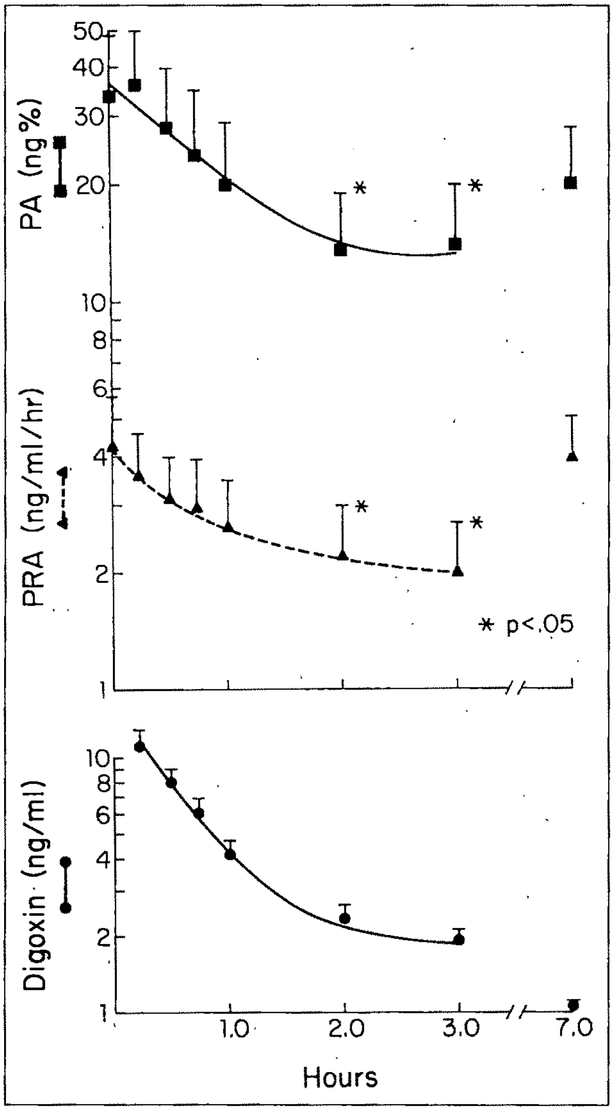

FIGURE 3. Acute response of plasma aldosterone (PA) and plasma renin activity (PRA) to bolus administration of digoxin (0.50 ng) in patients not receiving oral digoxin therapy. The serum digoxin concentration is also given. *p <0.05. (Reprinted from *Am J Med*.[15])

OPTIMIZING ORAL MEDICAL THERAPY

Digoxin: As more information accumulates, the age-old debate on the role of digoxin therapy is increasingly favoring use of the drug in the majority of heart failure patients with normal sinus rhythm. This has been largely supported by investigative studies,[12] as well as by large multicenter trials showing favorable effects of digoxin therapy.[13,14] Further, digoxin has additional therapeutic mechanisms, including suppression of the renin–angiotensin system (Figure 3),[15] and favorable resetting of autonomic tone.[16] In judging whether digoxin is optimal for a given patient, factors to be considered include determining the appropriate dose and indexing this to a specific serum digoxin concentration when appropriate. However, with progressive cardiac decompensation and subsequent refractory status, absorption can be adversely affected. Currently, the prospects for development of an alternative oral inotropic drug for long-term administration are not good. Recent data from the PROMISE trial suggest that agents such as the bipyridines actually increase morbidity and mortality in patients with functional class III–IV heart failure.[7]

Diuretic therapy: Although there is currently some debate regarding the appropriateness of diuretic use in patients with asymptomatic or mild LV dysfunction, there is no argument regarding such use in patients with refractory heart failure. With few exceptions, patients in this group will require diuretics. However, choosing the appropriate dose and deciding whether to use combined diuretic therapy require careful consideration. It is not unusual for a patient with CHF to become resistant to diuretics, and several variables such as renal insufficiency and aging can influence such resistance.[11,17] As renal dysfunction gradually progresses, a diuretic response may become progressively attenuated. Concomitant therapy with noncardiac drugs that affect renal function can also mitigate the diuretic response. Such agents include nonsalicylated anti-inflammatory drugs and indomethacin. Edema of the gastrointestinal tract can reduce drug absorption, thereby limiting efficacy. Different diuretic agents may act at different sites within the nephron, so that combination therapy, as discussed later, may be appropriate in the patient with developing refractory heart failure. At the very least, a patient should not be considered refractory to diuretics if receiving only moderate oral doses of a loop diuretic. Several approaches can help optimize diuretic therapy in refractory heart failure patients resistant to such therapy.[17] A single large bolus of intravenous diuretics may substantially improve urinary flow and natriuresis. Alternatively, frequent administration of smaller effective intravenous doses might achieve a cumulative effect. Although not typically used in practice, continuous intravenous infusion of a loop diuretic may prove efficacious.[18]

Perhaps the most versatile and effective approach to the management of such patients is administering the combination of a loop diuretic and thiazide diuretic. Long-term treatment with a loop diuretic can result in hypertrophy of the distal nephron segment,[19] producing enhanced sodium reabsorption. This can often attenuate the previous favorable response to a loop diuretic. To counter this, coadministration of a thiazide diuretic acting at the distal nephron can substantially increase net sodium and water excretion.

Intermittent administration of moderate doses of an intravenous loop diuretic to outpatients with sodium retention may promote sufficient diuresis to avoid hospitalization. This would also be particularly effective in the holding area of an emergency department. Continued moderation of sodium intake to avoid and/or manage refractory CHF should be emphasized. Animal studies[19] have shown that the response to a loop diuretic is often mitigated in animals that continue to ingest sodium ad lib compared with animals in whom sodium intake is somewhat restricted. Insistence that the patient ingest a moderate sodium diet enables the patient to participate in the therapeutic process.

If the patient remains resistant to diuretics, additional approaches may be considered, including further intensifying combined therapy. This might entail combining up to 3 diuretics (e.g., a loop and a thiazide diuretic and amiloride or spironolactone) that potentially act at different nephron sites. At least 1 report[20] in a limited number of patients suggests that spironolactone can be well tolerated even in combination with an ACE inhibitor. Although typically not required for refractory heart failure, ultrafiltration, hemofiltration,[21] hemodialysis, or peritoneal dialysis can be used for rapid removal of fluid. These modalities obviously will be important in treating cases of CHF accompanying chronic renal failure.[22]

Vasodilator therapy: In view of the results of recent trials, it now appears reasonable to treat any patient with functional class III or IV heart failure with an ACE inhibitor, hydralazine and isosorbide dinitrate, or a combination of these agents. Vasodilators continue to evolve. Newer vasodilators such as flosequinan offer promise in patients with CHF.[23] The different classes of vasodilators exert their effects by different mechanisms. This may account for some of the clinical findings in the VHeFT II,[5] in which the ACE inhibitor enalapril produced a relatively lower mortality rate yet the combination of hydralazine–isosorbide dinitrate improved exercise capacity and ejection fraction.

More novel approaches to the use of these drugs in refractory heart failure may be necessary. Varying combinations of these agents can be used intermittently, in sequence, etc. A patient who has become refractory to an ACE inhibitor, for example, may be given hydralazine–isosorbide dinitrate as a substitute, or vice versa.

When the patient with refractory heart failure who is currently taking digoxin, diuretics, and a vasodilator requires alteration in therapy, several issues should be considered. The first is drug dose. There is often a tendency for a "minimalist" approach to the use of vasodilators in heart failure because of concerns regarding excessive hypotension. Although it is certainly true that hypotension is an adverse effect of vasodilator therapy and is frequently seen in patients receiving ACE inhibitors, at the same time a reduction in blood pressure is anticipated. Guidelines helping to define an acceptable level of blood pressure have not been created. It is not unusual, however, to observe systolic blood pressure approximating 90 mm Hg with such therapy, and in the absence of significant orthostatic hypotension, such pressure is certainly acceptable. Pressures below this level may be tolerated in some patients but not in others.

The second issue is dosing interval. There is a perception that the once-a-day therapeutic philosophy that is advocated for treating hypertension is carried over for the treatment of the CHF population. It is important that vasodilator agents be given at the appropriate dosing interval. For ACE inhibitors such as captopril, therapy should be 3 times a day; for enalapril, therapy is typically twice a day, although once daily might be reasonable, particularly in the elderly patient.[24] Likewise, hydralazine therapy typically should be administered 3–4 times a day. Longer dosing intervals may result in ineffective vasodilator therapy.

Vasodilators that influence neurohormonal pathways (e.g., ACE inhibitors) may have a functional responsiveness related to these pathways. For instance, the extent of sodium restriction can have a considerable influence on response to an ACE inhibitor.[25]

Clinicians may consider the use of combined vasodilator therapy. Combination therapy does not imply giving 2 classes of agent at substandard doses rather than 1 agent at an appropriate therapeutic dose. Moreover, it should be emphasized that the excessive hypotension often potentiated by combined vasodilator therapy poses a serious obstacle to the successful management of these patients. If single-agent therapy is insufficient for management, then combined vasodilator therapy is a conceivable option if excessive hypotension can be avoided.

Therapy could be based on differences in mechanism of action. For example, a physician might elect to combine a direct-acting vasodilator with one that suppresses the neurohormonal axis (Figure 4).[26] Again, caution must be exercised, as excessive hypotension may be exacerbated by this combination.

Combined vasodilator therapy can also be determined based on disease substrate. Not all refractory heart failure is of the same etiology. In coronary artery disease, for instance, one could conceivably combine an ACE inhibitor with a calcium antagonist. Although calcium antagonists have caused unexpected cardiac decompensation in some patients with functional class III or IV heart failure, their use, particularly at lower doses, in combination with an ACE inhibitor may represent a pragmatic approach to the management of patients with known coronary artery disease. Hypertension may be ongoing in many patients with heart failure. In such patients, combining an ACE inhibitor with virtually any vasodilator known to be effective in hypertension, including calcium antagonists, would be reasonable. As previously discussed, hypertension in the CHF setting should be treated aggressively. This means reducing systolic blood pressure to 120–130 mm Hg and diastolic blood pressure to a level well below 90 mm Hg when possible.

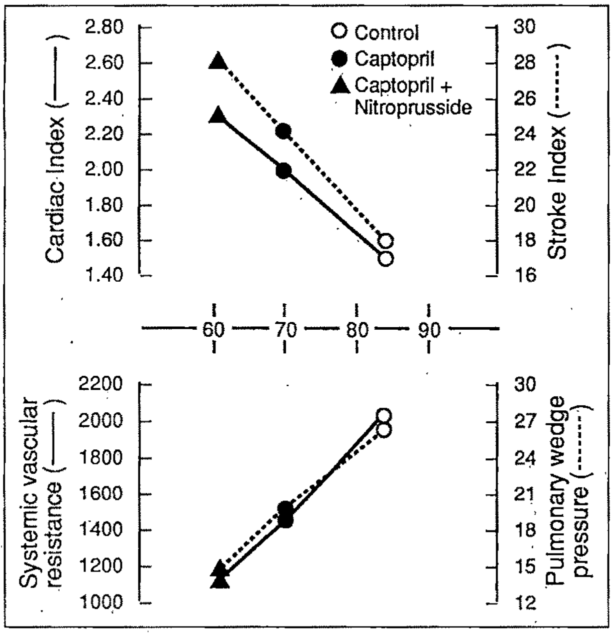

FIGURE 4. Data from acute studies demonstrating potential additive benefit of combining vasodilators that act by different mechanisms. Mean arterial pressure (mm Hg) is represented on the horizontal axis. In 11 patients with severe chronic congestive heart failure, captopril 25 mg was given orally. At peak response, nitroprusside was titered to reduce mean arterial pressure an additional 10%. This resulted in further increase of cardiac index (liters/min/m²) and stroke volume index (mL/beat) and reduction of systemic vascular resistance (dynes/s/cm⁵) and pulmonary wedge pressure (mm Hg). (Reprinted with permission from *Am Heart J*.[26])

Mitral regurgitation is a functional consideration that may be particularly important in patients with refractory CHF. In such cases, hydralazine would be effective. The marked reduction in systemic vascular resistance achieved by this agent can be greater than that observed with an ACE inhibitor and could conceivably have a much greater impact on reducing the regurgitant mitral fraction. With addition of sufficient ACE-inhibitor therapy to suppress the neurohormonal axis, hydralazine could become a mainstay of vasodilator therapy in such patients. It has been difficult, however, to calculate an appropriate end point for reduction of regurgitant fraction to serve as a guideline for therapeutic intervention. New modalities such as color-flow Doppler will be useful in this regard.

Hospital-based intravenous inotropic support: When the refractory CHF patient does not respond to all of the careful attempts at modulation of clinical status and therapy as outlined above, it is reasonable to consider hospitalization and administration of short-term intravenous inotropic support. Current oral therapy can be discontinued or stabilized with an eye toward restructuring therapy prior to hospital discharge. One may also administer intravenous diuretics to manage excessive sodium retention.

Intravenous inotropic support would consist of dobutamine infusions of 2.5–20 μg/kg/min. Typically, many patients respond to 7.5 or 10 μg/kg/min.[27] This therapy can be continued for 3–4 days, at which time the patient may be discharged. Data are lacking regarding the use of intravenous amrinone under these circumstances.

SUMMARY

Despite advances in the therapy of CHF, many patients still present with refractory symptoms and findings. If a logical approach is taken in the management of such patients, heroic and less available forms of therapy such as cardiac transplantation can often be avoided or delayed. A logical approach, therefore, would include the following: Administration of digoxin, diuretics, and a vasodilator on a chronic basis to all patients with NYHA functional class III–IV CHF, particularly those who continue to have symptoms. When a patient experiences cardiac decompensation despite this approach, the physician should assess the potentially changing clinical status and pathophysiology of the heart failure and optimize oral drug therapy. Should these 2 steps prove insufficient, hospital-based intravenous inotropic support, often in combination with intravenous diuretic therapy, should be considered to permit restructuring of a subsequent oral regimen.

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DISCUSSION

Dr. Lewis: The deleterious effect of mitral regurgitation in patients with refractory congestive heart failure (CHF) is often a lot more extensive than one might have thought. I have seen many cases in which patients have not received optimal diuresis. They look a lot better, but they still retain 10–15 pounds of fluid. Sometimes it is worth pushing that modality until you are sure you have reduced the mitral regurgitation as much as possible.

Dr. Cody: One thing I have become impressed with in the color-flow Doppler era is how unreliable the mitral regurgitation murmur can be in quantitating mitral regurgitation. By physical examination, it is very difficult to estimate the severity of mitral insufficiency. In this patient population, I almost automatically conduct a color-flow Doppler study to see if there is severe mitral regurgitation and make that a major focus of therapy.

Dr. Packer: Some studies[1] have shown that much of the improvement in hemodynamics that occurs with direct-acting vasodilators is due to reversal of mitral regurgitation and not to an improvement in systolic ejection fraction resulting from a reduction and improvement in loading conditions. It is a consistent finding.

This raises the question, what do you do with someone who has an ejection fraction of 12%, a markedly dilated left ventricle (LV), and secondary but significant mitral regurgitation? We grapple with this all the time, almost invariably thinking of reasons not to recommend surgical procedures because of the risk and questionable benefit. I think there may be a certain percentage of people whom we doom to medical therapy when they might, in fact, better benefit from mitral valve replacement or repair.

Dr. Gheorghiade: Mitral insufficiency in patients with severe systolic dysfunction is not so much related to size of the ventricle as to its shape.[2] Shape of the ventricle is also important in determining prognosis[3,4] and an important determinant of hemodynamic response to inotropic therapy.[5,6] Since mitral regurgitation in these patients is a dynamic process, it is doubtful that replacing the valve is of benefit.

Dr. Packer: Obviously, the assumption is that these patients are not surgical candidates, and we generally do not operate; but occasionally we have, and we have had significant postoperative success, enough to impress us that it is a question worth pursuing.

Dr. Creager: Transplantation is another option, if a donor heart is available. However, I think it is important to attempt to identify patients at risk long before they get into such dire straits.

Dr. Gheorghiade: Because of the severe shortage of donor hearts, it is important to identify patients with ischemic cardiomyopathy that might benefit from coronary artery bypass graft.[7] In addition, mitral valve repair, rather than replacement, should be performed, since this may preserve LV function.

Dr. Kelly: I think cardiologists and surgeons need to join in a prospective trial about whether preservation of papillary muscle with valve replacement really does make a difference in preserving LV function. The feeling among surgeons is that clearly it does.

Dr. McCall: The key is to identify the patients who are going to do well with surgery.

Dr. Yusuf: Engelmeier et al[8] have shown that the use of β blockers dramatically improves the condition of even patients with severe heart failure. Few other groups have been able to reproduce these findings in patients with heart failure. One way of dealing with the mitral regurgitation problem may be by prolonging diastole and reducing the total period of systole by simply reducing heart rate with a β blocker.

Dr. Cody: I think β blockers should probably be used more frequently in NYHA functional class I and II heart failure. We certainly should reconsider using them in patients with LV dysfunction and following myocardial infarction, where calcium antagonists now appear to be favored for reasons that are not particularly clear. In functional class IV refractory heart failure we may still encounter more problems by using a β blocker, but this is under evaluation.

Dr. Creager: My feeling is that we can be of great assistance in teaching our house staff and referring physicians to be much more aggressive with their use of diuretics. Most tend to back off from using these agents far too soon. Appropriate use of diuretic therapy can cause an impressive clinical response, whether by adding a thiazide diuretic to a loop diuretic or by hospitalizing the patient and giving parenteral diuretics. Particularly in this circumstance, it is important that physicians remain cognizant about electrolyte disturbances, particularly hypokalemia, hypomagnesemia, and hyponatremia.

Dr. Cody: I find that to be particularly true with metolazone. I have had a bit more success with hydrochlorothiazide, but that is observational. However, there are very few primary studies in the heart failure literature on this issue.

Dr. Kelly: It is important to administer a short-acting diuretic like furosemide sufficiently frequently to obtain the desired clinical effect. One needs to get tubular levels up to a threshold where diuresis—and natriuresis—can be sustained. Most physicians give furosemide once or perhaps twice a day, but it should normally be given at least twice a day. If it is only given once a day, pharmacodynamic effects will occur that diminish the drug's effectiveness and a sustained negative sodium balance will not be obtained.

On the other hand, as I believe Dr. Cody pointed out, you should not go below a 20–30 mEq sodium diet. If you go below that, hyponatremia ensues, followed by severe hypokalemia due to renin and aldosterone activation.

Dr. Gheorghiade: Many of so-called "refractory-to-therapy" patients will respond by combining two diuretics (a loop diuretic with a thiazide diuretic or metolazone) or vasodilators, and ACE inhibitors with hydralazine and nitrates. It should also be recognized that improving hemodynamics in patients with end-stage CHF may also prolong life.[9] Also, patients with ongoing ischemia due to severe coronary artery disease and severe CHF may not respond to conventional therapy for heart failure.[10]

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Long-Term Strategies in the Management of Heart Failure: Looking Beyond Ventricular Function and Symptoms

Milton Packer, MD

Therapeutic approaches to the management of heart failure have traditionally focused on short-term hemodynamic and symptomatic goals, but present evidence suggests that most therapeutic decisions have long-term consequences. Treatment may change the rate of disease progression, modify the need for additional therapy, influence the number of hospitalizations, and alter the risk of death. However, there may be little relation between a drug's short-term effect on cardiac function or cardiovascular symptoms and its long-term effect on survival. Some therapeutic interventions favorably influence the outcome of patients with heart failure, even though they exert negative inotropic effects; others adversely affect the outcome of patients, even though they markedly improve cardiac performance. This discordance might be explained if the most important predictor of response to a therapeutic intervention in heart failure were the effect of the pharmacologic agent on neurohormonal systems rather than on hemodynamic variables. In general, drugs that decrease the effects of the sympathetic nervous system (digitalis glycosides) and the renin–angiotensin system (angiotensin-converting enzyme [ACE] inhibitors) reduce the risk of worsening heart failure. Conversely, drugs that potentiate the effects, or increase the activity, of the sympathetic nervous system (phosphodiesterase inhibitors) or the renin–angiotensin system (calcium antagonists) increase cardiovascular morbidity and mortality. These observations suggest that physicians should no longer focus on short-term hemodynamic or symptomatic goals in the treatment of heart failure but, instead, should manage patients to improve both the quality and quantity of life.

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For the last 50 years, the principal goal in the treatment of heart failure has been the relief of symptoms. If a patient experiences dyspnea or fatigue, the physician prescribes drugs to increase the amount of effort that the patient can tolerate before these symptoms develop. If a patient complains of fluid retention, the physician attempts to relieve the edema by administering drugs that reduce the swelling of the legs and abdomen. If these goals are achieved, both the patient and the physician consider the treatment to be successful. There is usually little discussion about the future; the patient is rarely told that his symptoms will recur or that heart failure is a progressive disorder. Hence, the approach to the patient with heart failure has been similar to the approach to the patient disabled by the pain of terminal cancer: the principal goal has been short-term relief of symptoms.

Why have we emphasized only short-term goals in management of heart failure? There are two reasons. First, 50 years ago, physicians thought that heart failure was only an acute disorder. Heart failure was present when patients sought urgent medical attention for pulmonary or peripheral edema; after these symptoms subsided, the patient no longer had heart failure. To be sure, physicians understood that the underlying cardiac disorder had not disappeared, but this disorder was not viewed as heart failure as long as there was no overt fluid retention. Second, even after heart failure was recognized as a chronic disorder, physicians generally doubted they could change its natural history. Clinical experience suggested that the underlying disease progressed regardless of what treatment was prescribed. Simply put, cardiologists believed that they could do as much for patients with heart failure as oncologists could do for patients with terminal cancer.

During the last decade, however, many studies have challenged the assumption that physicians can do little to alter the clinical course of heart failure. We now know that treatment may change the rate of disease progression, modify the need for

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additional therapy, influence the number of hospitalizations, and alter the risk of death. Importantly, there may be little relation between a drug's effect on cardiac function or cardiovascular symptoms and its effect on survival.[1] This point is well illustrated by examining the effect of various therapeutic agents on the natural history of heart failure.

THE NATURAL HISTORY OF HEART FAILURE

Effect of vasodilator drugs: Vasodilators should exert favorable effects on the natural history of heart failure, since antagonism of peripheral vasoconstriction reduces wall stress and thereby minimizes the rate of structural remodeling that is responsible for the inexorable deterioration of ventricular function.[2,3] This concept has been supported by studies using different vasodilators in experimental models of heart failure.[4,5] Based on these studies, similar results were expected when vasodilators were evaluated in the clinical setting.

At first, these expectations seemed to be borne out by the results of controlled clinical trials. The first Veterans Affairs Vasodilator–Heart Failure Trial (V-DHeFT) demonstrated that a combination of two direct-acting vasodilators (hydralazine and isosorbide dinitrate) reduced mortality in patients with mild-to-moderate heart failure.[6] In the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS) and Studies of Left Ventricular Dysfunction (SOLVD),[7,8] the angiotensin-converting enzyme (ACE) inhibitor enalapril reduced the risk of worsening heart failure, the frequency of hospital visits, and the mortality in patients with mild, moderate, and severe symptoms. Favorable effects on disease progression and mortality have also been observed with other ACE inhibitors (e.g., captopril).[9,10] These findings suggested that any vasodilator that reduces hemodynamic stress should reduce the morbidity and mortality of chronic heart failure.

However, not all vasodilators have favorably influenced the natural history of heart failure. Prazosin did not reduce mortality in the V-HeFT study, even though treatment with the drug was associated with significant long-term vasodilator effects.[6] Some vasodilators have produced long-term adverse effects. For example, despite beneficial effects on cardiac performance, minoxidil increased the need for diuretics and enhanced cardiovascular morbidity in a placebo-controlled trial.[11] Similarly, despite favorable short-term hemodynamic effects, many calcium antagonists increase the risk of worsening heart failure and cardiovascular death in patients with advanced left ventricular dysfunction.[12–15]

The results of these studies indicate that vasodilators can change the natural history of heart failure, but the nature of their effects cannot be accurately predicted by their actions on peripheral blood vessels. What characteristic should a vasodilator possess to exert favorable long-term effects in heart failure? The answer to this question has emerged from comparative studies of vasodilators. Controlled clinical trials have shown that captopril produces more favorable effects on the clinical and hemodynamic status of heart failure patients than nifedipine or prazosin,[16–18] and that both captopril and enalapril produce a greater reduction in mortality than hydralazine or isosorbide dinitrate, alone or in combination.[19–21] What unique quality is possessed by the ACE inhibitors? Whereas prazosin, minoxidil, and the calcium antagonists stimulate the renin–angiotensin system,[16,21–24] ACE inhibitors act by reducing the formation of angiotensin-II. This difference in the neurohormonal response to treatment may be critical, given the central role of the renin–angiotensin system in the progression of heart failure.[25,26]

Effect of inotropic agents: Positive inotropic agents should have favorable effects on the natural history of heart failure, since a decrease in cardiac contractility is generally recognized as a fundamental defect in heart failure. Further, any drug that improves systolic ejection also reduces ventricular wall stress, particularly if the positive inotropic agent also dilates peripheral blood vessels. Most positive inotropic drugs have such combined characteristics. Digitalis glycosides not only increase the inotropic state of the failing heart, but dilate blood vessels by virtue of their inhibition of sympathetically mediated vasoconstriction.[27] Similarly, β-agonists and phosphodiesterase inhibitors exert both positive inotropic and vasodilator effects by virtue of their ability to increase intracellular cyclic adenosine monophosphate (cAMP).[28,29] Regardless of how it is achieved, the combination of positive inotropic and vasodilator effects should favorably influence the long-term outcome of heart failure. The validity of this hypothesis has been demonstrated with both digitalis glycosides and the phosphodiesterase inhibitors in experimental models of heart failure.[30,31] Based on these observations, it was expected that similar results would be observed in the clinical setting.

As in the case of vasodilators, these expectations were initially borne out by the results of controlled clinical trials. Several studies have shown that digitalis glycosides have salutary clinical effects in patients with chronic heart failure in normal sinus rhythm. In patients with mild-to-moderate symptoms not receiving the drug, the addition of digoxin reduces the number of hospital visits for worsening heart failure and the need for increasing doses of diuretics.[32] In patients with moderate-to-severe symptoms already receiving the drug, digoxin withdrawal is predictably accompanied by clinical deterioration, which may not be prevented by the addition of other therapeutic agents.[33–35] Digoxin reduces the risk of worsening heart failure whether or not patients are receiving ACE inhibitors.[34,35] These findings suggested that any drug that enhances contractility could be expected to reduce the morbidity and mortality of chronic heart failure.

However, not all positive inotropic agents have produced favorable effects on the natural history of heart failure. Although β-agonists and phosphodiesterase inhibitors produce hemodynamic effects that are superior to those of digitalis glycosides, a meta-analysis of controlled trials suggested that long-term therapy with these drugs may increase mortality of patients with mild-to-moderate heart failure.[36] In the Prospective Randomized Milrinone Survival Evaluation (PROMISE), giving milrinone to patients with severe heart failure was associated with a significant increase in all-cause mortality and risk of cardiovascular death, as well as an increase in frequency of hospitalizations for cardiovascular causes.[37] Similar results have been reported with other phosphodiesterase inhibitors.[38,39]

The results of these studies indicate that positive inotropic agents can change the natural history of heart failure, but the nature of their effects cannot be accurately predicted by their actions on ventricular function. What characteristic should a positive inotropic agent have to exert favorable long-term effects in heart failure? Whereas both β-agonists and phosphodiesterase inhibitors increase myocardial levels of cAMP, digitalis glycosides tend to decrease these levels because of their ability to inhibit the outflow of sympathetic impulses from the central nervous system.[27] This difference in the neurohormonal response to treatment may be critical, given the central role of the sympathetic nervous system in the progression of heart failure.[26] In that sense, the actions of digitalis glycosides may resemble those of other sympathetic antagonists (β-blockers), which may also favorably influence the natural history of patients with ischemic left ventricular dysfunction.[40,41]

CLINICAL IMPLICATIONS

Based on the studies cited, both vasodilators and positive inotropic drugs can alter the natural history of heart failure, but there seems to be little relation between the effects of these drugs on hemodynamic variables and the effects of these drugs on survival. Some vasodilators favorably influence the outcome of patients with heart failure, even though they exert negative inotropic effects[40,41]; others adversely affect the outcome of patients, even though they markedly improve cardiac performance.[11] Similarly, digitalis glycosides have more favorable effects on the clinical course of heart failure than the phosphodiesterase inhibitors,[33] even though cAMP-dependent agents affect cardiac contractility and peripheral vasculature more favorably than digitalis glycosides.

The results of these studies suggest that the most important predictor of response to therapeutic intervention in heart failure is its effect on neurohormonal systems. In general, drugs that decrease the effects of the sympathetic nervous system (digitalis glycosides) and the renin–angiotensin system (ACE inhibitors) reduce the risk of worsening heart failure and the need for increasing doses of diuretics. Conversely, drugs that potentiate the effects or increase the activity of the sympathetic nervous system (phosphodiesterase inhibitors) or the renin–angiotensin system (calcium antagonists) increase cardiovascular morbidity and mortality. These conclusions are consistent with experimental observations that neurohormonal systems exert direct deleterious effects on the heart that are independent of their hemodynamic effects.[42,43] The modulating effects of drugs on the neurohormonal system may be particularly important in patients with heart failure who are given diuretics, since such agents may be one of the most important and earliest causes of neurohormonal activation in patients with left ventricular dysfunction.[44]

These studies indicate that we can no longer use hemodynamic goals as the basis of treatment for patients with heart failure, since therapeutic decisions may influence the neurohormonal system and thus the long-term outcome of patients independently of a drug's effect on ventricular function. Hence it is possible for physicians to improve hemodynamic variables and control the symptoms of heart failure but make decisions that adversely affect the patient's survival.

What mistakes can be made? On the one hand, we may innocently treat associated conditions in patients with heart failure with drugs that have established adverse effects on survival. Typically, this occurs in patients with heart failure when we treat myocardial ischemia with calcium antagonists[15] and ventricular arrhythmias with class-I antiarrhythmic drugs.[45] On the other hand, we may also err by withholding treatment with drugs that have established beneficial effects on survival. This may occur when we decide *not* to use ACE inhibitors in patients with chronic heart failure whose symptoms are adequately controlled with diuretics. Hence, both errors of omission and errors of commission may be committed when we make therapeutic decisions based on how well patients are doing at any given moment. Physicians should no longer focus on short-term hemodynamic or symptomatic goals in the treatment of heart failure but, instead, should manage patients to improve both the quality and quantity of life.

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DISCUSSION

Dr. Creager: Dr. Packer, you suggested looking at pharmacologic agents in terms of their effects on neurohormonal systems. What do you think are the adverse consequences of neurohormonal activation?

Dr. Packer: The simplistic thing to say would be that neurohormonal activation exerts a direct toxic effect on the myocardium. In vitro, that is true. Certainly in animal models that is true. However, I think the specific effects of neurohormonal activation are far more complex.

Dr. Creager: I am not so sure that is completely true. Clearly, if you raise plasma norepinephrine levels to a critically high level, such as is seen in pheochromocytomas, you may cause direct myocardial necrosis. But I am not aware of any evidence that the levels we commonly see in heart failure are directly toxic to the myocardium. Flooding the system with angiotensin II has a lot of effects—it has morphologic effects to mitogen—but I am not sure that this will cause myocyte necrosis.

Dr. Mancia: There is evidence that in patients with stroke, plasma creatinine kinase is elevated and that a reduction is obtained by β blockade. So there can be a number of situations in which catecholamine levels are high—and this can be associated with some necrotic effect on the myocardium.

Dr. Packer: One thought that has always disturbed me is that all the models that have looked at the potential toxic effects of circulating neurohormones have evaluated normal hearts. It is possible that the heart that is dilated and fibrotic may be more susceptible to the toxic effects of these substances.

Dr. Mancia: Plasma norepinephrine levels are a somewhat fallible index of sympathetic activity in general. This may be equally the case in congestive heart failure, because in this condition perhaps 50% of plasma norepinephrine is determined by the clearance of norepinephrine. It could well be that a drug that increases renal blood flow and function reduces norepinephrine levels simply by increasing norepinephrine clearance, not by decreasing the sympathetic nerve flow.

Dr. Ferguson: In 3 different studies with nifedipine, we looked at heart rate responses to arterial baroreceptor perturbation, vasoconstrictor responses to cardiac baroreceptor unloading, and nerve traffic responses. We found that nifedipine potentiates both arterial and cardiopulmonary baroreflex control of vascular resistance, sympathetic traffic, and heart rate. It may be that the negative inotropic properties of nifedipine outweigh its potential in neurosynthesizing actions.

All calcium antagonists are not the same as far as the baroreceptors are concerned. In animals, nifedipine will acutely potentiate single-fiber carotid-sinus nerve responses, whereas verapamil has the opposite effect.

Dr. Gheorghiade: In addition to neurohumoral activation, hemodynamics will continue to be an important target for therapeutic interventions. Therapy may decrease the excessive and detrimental neurohumoral activation directly, or indirectly by improving hemodynamic abnormalities. The key is to improve hemodynamics in heart failure not at the expense of increasing neurohumoral activation. If medical therapy will decrease the neurohumoral activation without improving hemodynamics, many patients may decompensate clinically. The improvement in hemodynamics should proceed, pari pasu, with a decrease in neurohumoral activation.

Dr. Creager: Has anyone ever given clonidine and looked at heart failure, either symptomatic or any other way?

Dr. Packer: Clonidine reduces circulating levels of norepinephrine, at least in the short term, and this is accompanied by a negative inotropic effect. However, there are no long-term controlled trials with clonidine in patients with chronic heart failure, and as is the case with β blockers, the short- and long-term effect of sympathetic inhibitors may differ.

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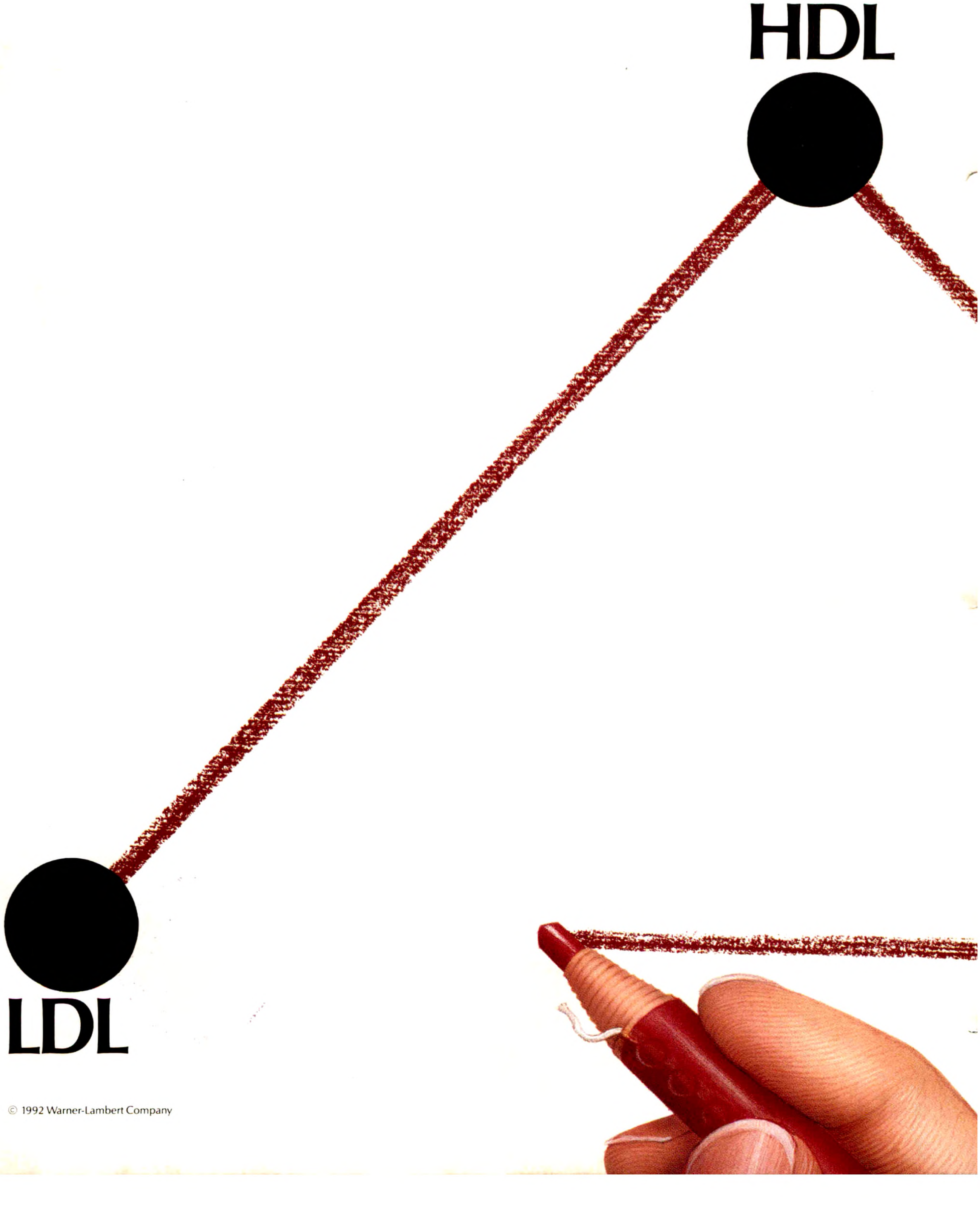

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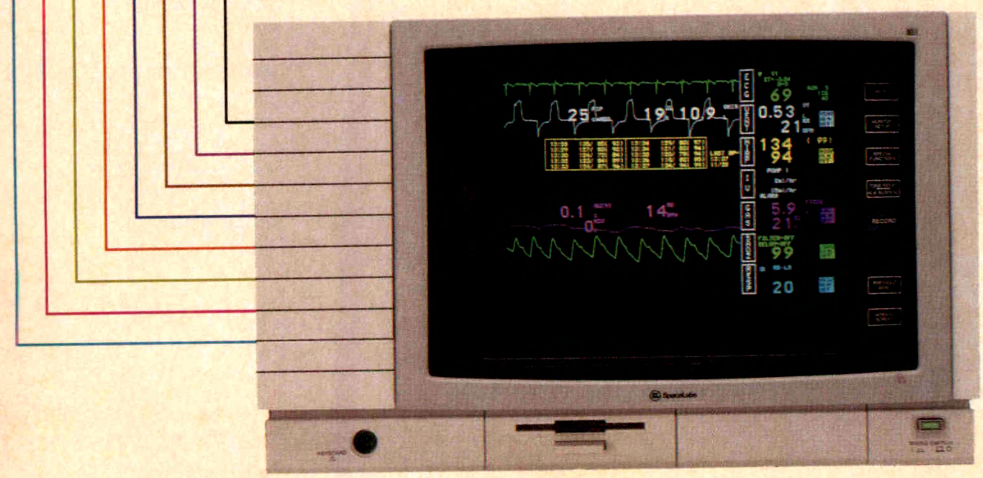

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CORONARY ARTERY DISEASE

1517

Mechanism of Exercise-Induced Hypotension in Coronary Artery Disease

Abdulmassih S. Iskandrian, Jeffrey G. Kegel, Joseph Lemlek, Jaekyeong Heo, Virginia Cave, and Basil Iskandrian

The mechanism of hypotension was examined in 25 patients with coronary artery disease (CAD) who developed hypotension during treadmill exercise testing (group 1) and was compared with the results of a group of 25 CAD patients who had normal pressure response to exercise (group 2). The 2 groups were comparable in age, sex, extent of CAD, previous myocardial infarction, left ventricular ejection fraction, history of hypertension, and cardiac medications. ST-segment depression occurred in 44% of patients in group 1 and in 52% in group 2 (p = not significant [NS]), and angina during exercise occurred in 56% in group 1 and in 44% in group 2 (p = NS). Thallium images were abnormal in 24 patients (96%) in group 1 and in 20 (80%) in group 2 (p = NS). Percent thallium abnormality and severity of thallium abnormality were similar in the 2 groups. Ischemia involving the inferior/posterior segments was seen in 68% of patients in group 1 and in 60% in group 2. Thus, exercise-induced hypotension cannot be explained by the extent of CAD or ischemia; it is probably due to ischemic activation of mechanoreceptors, a mechanism similar to those of other types of neurally mediated hypotension.

1521

Frequency and Predictors of Left Ventricular Segmental Dysfunction in Patients with Recent Rest Angina

Mark F. Warner, Germano DiSciascio, Ravinder Kohli, M. Nagui Sabri, Evelyne Goudreau, Michael J. Cowley, and George W. Vetrovec

Fifty-two patients with rest angina and no evidence of myocardial necrosis who underwent cardiac catheterization within 3 days of the last episode of chest pain were examined. A "culprit" lesion responsible for the ischemic episode was identified and analyzed in each patient. Segmental postischemic left ventricular dysfunction was present in 58% of patients. It occurred significantly more often with lesion location in the left anterior descending artery and less often with involvement of the circumflex. Electrocardiographic evidence of ischemia was seen in 75% of patients and was more sensitive for left ventricular dysfunction when the vessel involved was the left anterior descending or right coronary artery.

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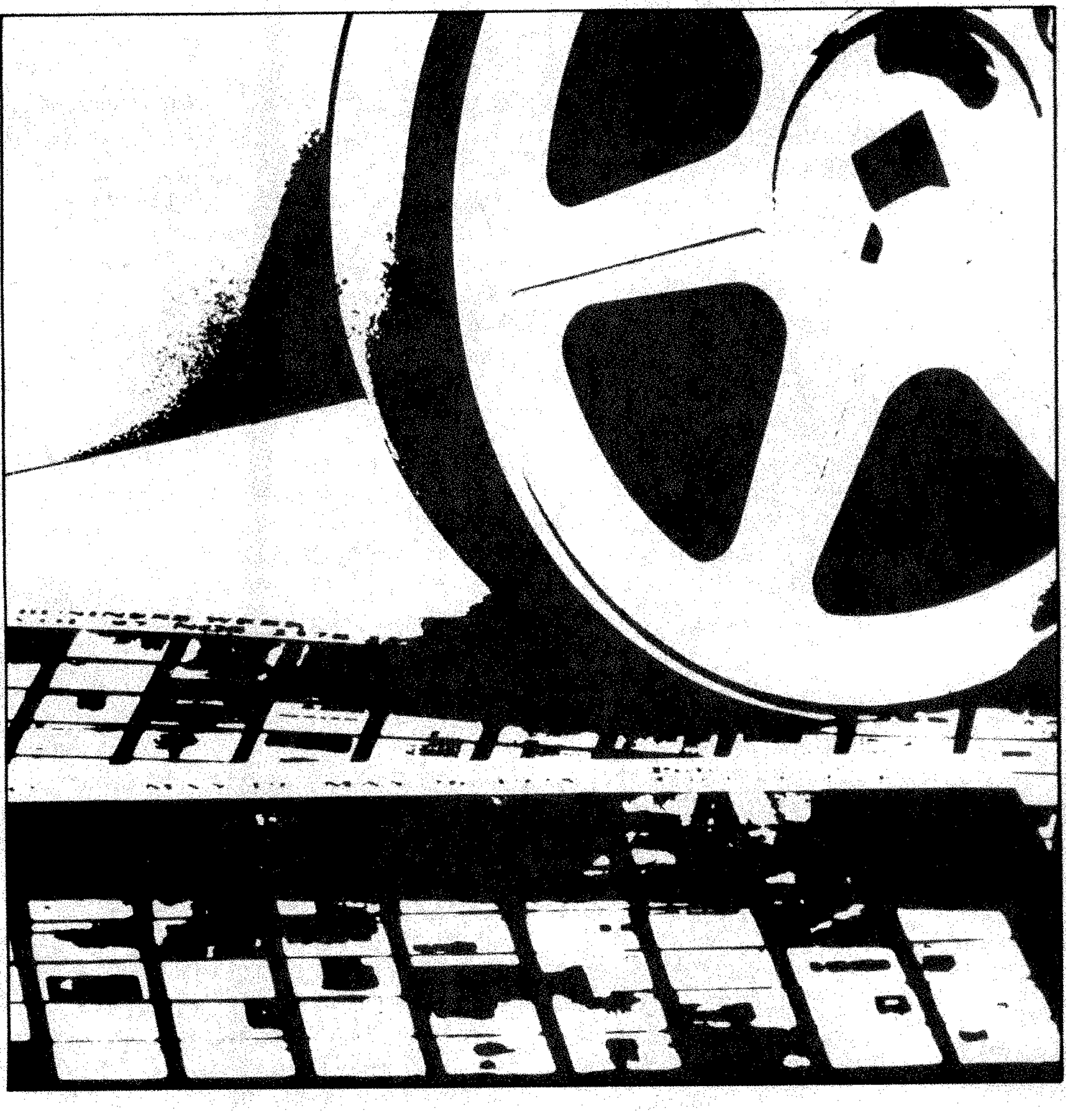

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Acute and Long-Term Effects on Myocardial Ischemia of Intermittent and Continuous Transdermal Nitrate Therapy in Stable Angina

M. Juhani Knuuti, Martine Wahl, Ingela Wiklund, Paul Smith, Liisa Alhainen, Risto Härkönen, Pekka Puska, and Dan Tzivoni

The aim of the study was to assess the efficacy and safety of continuous and intermittent transdermal nitrate therapy using Holter monitoring. Eighty-five patients with stable angina pectoris participated in an open trial lasting 12 weeks. Patients were randomized to either continuous- or intermittent-therapy groups. Forty-eight-hour Holter monitoring was performed after randomization, and again after 2 and 12 weeks. The number of ischemic episodes per 48 hours were 3.1 ± 0.7 (mean ± SEM), 1.8 ± 0.4 at 2 weeks and 2.0 ± 0.6 at 12 weeks in the intermittent-therapy group and 3.8 ± 1.1, 3.5 ± 0.9 and 4.2 ± 1.2, respectively, in the continuous-therapy group. No changes and differences between the treatment groups were seen in nighttime episodes. Our results suggest that intermittent transdermal nitrate therapy is superior to continuous therapy in reducing ischemic episodes. The nighttime nitrate-free interval does not lead to increased ischemia during patients concomitant antiischemic medication.

1533

Immediate and Follow-Up Results of the Conservative Coronary Angioplasty Strategy for Unstable Angina Pectoris

Francis Stammen, Ivan De Scheerder, James J. Glazier, Johan Van Lierde, Matty Vrolix, Jos L. Willems, Hilaire De Geest, and Jan Piessens

Of 1,421 consecutive patients without previous myocardial infarction undergoing a first coronary angioplasty, 631 (study group) had unstable and 790 (control group) had stable anginal symptoms at hospital admission. In all study patients, angioplasty was performed only after intense efforts to medically stabilize symptoms. An almost equally favorable primary success rate was achieved in the study and control patients (91.7 and 94.4%, respectively; p = not significant). There was a slightly greater incidence of all adverse in-hospital events in the study group (9 vs 5.9%; $p < 0.04$). During a minimum follow-up of 6 months, there were no significant differences in the rates of adverse events between the 2 groups. The data suggest that in patients with unstable angina, a conservative angioplasty strategy results in similarly favorable immediate and short-term outcomes compared with those in patients with stable angina.

1538

Echocardiographic Algorithms for Admission and Predischarge Prediction of Mortality in Acute Myocardial Infarction

Jens Berning, Jeppe Launbjerg, and Merete Appleyard

Optimized prognostic algorithms for routine bedside use in acute myocardial infarction (AMI) were developed based on clinical examination and an early (<72 hours after AMI) echocardiographic estimate of left ven-

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tricular ejection fraction in 201 consecutive patients. A Cox model was used for identification of the most predictive combination of clinical and echocardiographic variables concerning mortality. The following 2 algorithms were developed for use on admission and predischarge, respectively: mortality at 2 months $= 1 - \exp - [0.051 \times \exp[0.044 \times (\text{age} - 60) - 0.117 \times (\text{LVEF} - 40)]]$; and mortality at 1 year $= 1 - \exp - [0.101 \times \exp[0.408 \times (\text{maxKillip } 1) - 0.061 \times (\text{LVEF} - 40)]]$. The validity of the predischarge algorithm was confirmed by testing in an independent population of 195 patients with AMI. The proposed clinicoechocardiographic algorithms appear to help maximize early risk stratification after AMI with minimal effort.

1545

Electrocardiographic Criteria for Diagnosis of Acute Myocardial Infarction in Childhood

Jeffrey A. Towbin, J. Timothy Bricker, and Arthur Garson, Jr.

Electrocardiographic criteria for myocardial infarction (MI) in adults are well known and accepted, but no general criteria exist for children. We report 37 autopsy-proved cases of transmural MI and electrocardiographic evidence of infarction in 30 of these cases. A variety of conditions previously reported to produce "pseudo-infarctions" are included in these cases of MI. Compilation of the electrocardiographic data in all patients allowed for the development of criteria for the diagnosis of MI in childhood, and include wide Q waves (>35 ms) with or without Q-wave notching, ST-segment elevation (>2 mm), and prolonged QT interval corrected for heart rate (QTc >440 ms) with accompanying Q-wave abnormalities. With use of these electrocardiographic criteria, an additional 19 patients were subsequently diagnosed prospectively with MI; 3 of these children died. Pathologic evaluation confirmed the electrocardiographic diagnosis of MI.

1549

Frequency of Coronary Artery Disease and Left Ventricular Dysfunction in Cocaine Users

Anil Om, Mark Warner, Nagui Sabri, Laura Cecich, and George Vetrovec

Thirty-three patients with history of cocaine use and cardiac symptoms were angiographically evaluated. Twenty patients (60%) had coronary artery disease (CAD) despite young age and relatively low cardiovascular risk factors. Fifteen patients had normal left ventricular ejection fraction, 12 had between 30 and 50%, and 6 had ≤30%. Twelve patients with ejection fraction ≤50% had CAD and segmental wall motion abnormalities, whereas the other 6 had normal coronary arteries. These data suggest that chest pain suggestive of angina related to cocaine use (even in young patients) warrants further evaluation to detect the presence of CAD, and that myocardial dysfunction in such patients could be of ischemic and nonischemic etiology.

1553

Preoperative Coronary Artery Disease Risk Stratification Based on Dipyridamole Imaging and a Simple Three-Step, Three-Segment Model for Patients Undergoing Noncardiac Vascular Surgery or Major General Surgery

Jean Lette, David Waters, Michel Cerino, Michel Picard, Patrick Champagne, and Jacques Lapointe

A simple 3-step, 3-segment scintigraphic model was developed to improve the accuracy of dipyridamole thallium imaging for preoperative cardiac risk assessment. Step 1: The postoperative cardiac event (infarction or cardiac death) rate was 1.3% in 355 patients with normal anterior, inferior and posterolateral segment perfusion and without transient left ventricular dipyridamole-induced cavitary dilation. Step 2: Of 29 patients with either reversible defects of all 3 segments, transient cavitary dilation, or at least 1 severe reversible defect, 52% sustained a postoperative cardiac event. Step 3: The remaining 101 patients were stratified according to age, diabetes and the number of segments displaying reversible defects with event rates ranging from 5 to 36%.

SYSTEMIC HYPERTENSION

1559

Effects of Sustained-Release Nicardipine on Regression of Left Ventricular Hypertrophy in Systemic Hypertension

Howard C. Dittrich, Joshua Adler, James Ong, Martha Reitman, Michael Weber, and Michael Ziegler

The effects of sustained-release nicardipine on neurohumoral and Doppler echocardiographic parameters were studied in a double-blind placebo controlled trial of 28 patients with mild to moderate systemic hypertension. Blood pressure was decreased significantly at 6 weeks. Nicardipine caused some neurohumoral stimulation after the first dose but there was no evidence for stimulation of these parameters after 6 weeks. No significant differences in Doppler measures of mitral inflow or echocardiographic measures of left ventricular (LV) function, wall thickness or mass were noted in the 6-week phase of the study. In a subgroup of 13 patients treated for 1 year, systemic pressure remained significantly decreased. Concomitantly, both septal and posterior wall thickness decreased significantly as did LV mass index. No improvement in Doppler indexes of diastolic function was noted. Regression of LV hypertrophy occurs with long-term nicardipine therapy, which may be possible because of the lack of sustained neurohumoral stimulation by this agent.

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CONGESTIVE HEART FAILURE

1565

Anaerobic Threshold Detection in Patients with Congestive Heart Failure

Stuart D. Katz, Robert Berkowitz, and Thierry H. LeJemtel

Anaerobic threshold measurements determined either invasively by analysis of arterial lactate concentration (lactate threshold) or noninvasively by respiratory gas exchange analysis (ventilatory threshold) were compared in 16 patients with chronic congestive heart failure (CHF) (New York Heart Association functional class II–III). In patients with severe CHF (peak oxygen uptake <12 ml/kg/min), lactate threshold could not be detected. In patients with mild to moderate CHF (peak oxygen uptake >14 ml/kg/min), lactate and ventilatory thresholds were closely related.

1570

Left Ventricular Dysfunction Due to Atrial Fibrillation in Patients Initially Believed to Have Idiopathic Dilated Cardiomyopathy

Martha Grogan, Hugh C. Smith, Bernard J. Gersh, and Douglas L. Wood

Ten patients with severe left ventricular dysfunction and atrial fibrillation with rapid ventricular response who initially were believed to have idiopathic dilated cardiomyopathy were evaluated after therapy. All patients presented with symptomatic heart failure; initial left ventricular ejection fraction ranged from 12 to 30% (median 25). With ventricular rate control or conversion to sinus rhythm, all patients became asymptomatic, and ejection fractions ranged from 40 to 64% (median 52). It is suggested that atrial fibrillation with rapid ventricular response may be a primary cause of severe ventricular dysfunction and that the "cardiomyopathy" may be completely reversible.

1574

Myocardial Adenine Nucleotide Concentrations and Myocardial Norepinephrine Content in Patients with Heart Failure Secondary to Idiopathic Dilated or Ischemic Cardiomyopathy

Vera Regitz and Eckart Fleck

To assess myocardial energy metabolism in heart failure, myocardial adenosine triphosphate (ATP), diphosphate and monophosphate were measured in endomyocardial biopsy specimens from 19 patients with dilated and 11 with ischemic cardiomyopathy in comparison with those of normal control subjects. Myocardial norepinephrine was quantitated simultaneously in the same biopsy specimens to determine if the myocardium studied was metabolically affected. In 19 patients with dilated and 11 with ischemic cardiomyopathy, myocardial total adenine nucleotides as well as ATP levels were unchanged in comparison with those in control subjects (total adenine nucleotides [in nmols/mg of noncollagen protein]: dilated 39 ± 3, ischemic 30 ± 3 and controls 37 ± 4; and ATP: dilated 23 ± 3, ischemic 19 ± 3 and controls 23 ± 3). Myocardial norepinephrine in the same biopsy specimens from heart failure patients was significantly decreased (dilated 5.8 ± 1.1, ischemic 5.7 ± 1.3 and controls 12 ± 1.1

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pg/μg of noncollagen protein). Thus, reduced myocardial adenine nucleotides are not an early metabolic feature of heart failure.

1581

Use of Limb Movement Sensors as Indicators of the Level of Everyday Physical Activity in Chronic Congestive Heart Failure

Simon W. Davies, Sally L. Jordan, and David P. Lipkin

A lightweight movement sensor worn on the wrist or ankle, which provides a cumulative record of limb movement was evaluated. The sensor counted reliably when tested in a laboratory rig and during treadmill exercise. Twenty-four hour movement scores in 30 patients with stable chronic heart failure were lower than in 20 age-matched control subjects ($p < 0.005$), and correlated with a standard questionnaire for everyday physical activity ($R = +0.72$, $p < 0.001$). The correlation between movement scores and treadmill exercise capacity (peak oxygen consumption on maximal exercise) was weak ($R = +0.42$, $p = 0.01$). Quality-of-life score correlated with movement scores ($R = +0.53$, $p < 0.002$) but not with peak oxygen consumption ($R = +0.36$, p = not significant). Thus, the level of everyday physical activity may be more relevant to the patient's quality of life than is treadmill exercise capacity, and the movement monitors may be valuable to assess functional status and the response to therapies.

1587

Effect of Quinapril on Blood Pressure and Heart Rate in Congestive Heart Failure

Jonathan N. Townend, John N. West, Michael K. Davies, and William A. Littler

The effect of angiotensin-converting enzyme inhibitor therapy with quinapril on 24-hour ambulatory intraarterial blood pressure (BP) and heart rate (HR) was studied in 12 patients with severe congestive heart failure. The decrease in BP was small and unlikely to jeopardize vital organ perfusion. The profile of 24-hour BP was not changed but there was an increase in diurnal variation in HR. HR variability as measured by the interquartile difference (75th − 25th percentile of the frequency distribution of RR intervals) increased significantly with quinapril (91 to 134 ms, $p = 0.008$). The variability of successive differences between RR intervals, an index of vagal activity, also increased significantly (interquartile difference, 17 ms at baseline and 31 ms with quinapril, $p = 0.02$). The increase in HR variability is likely to be due to an increase in vagal tone as a result of a reduction in circulating angiotensin II.

1591

Effectiveness of Preload Reserve as a Determinant of Clinical Status in Patients with Left Ventricular Systolic Dysfunction

Marvin A. Konstam, Marvin W. Kronenberg, James E. Udelson, Debra Kinan, Jeanne Metherall, Noreen Dolan, Tonya Edens, Donna Howe, Lori Kilcoyne, Claude Benedict, Marston Youngblood, Joan Barrett, Salim Yusuf, for the SOLVD Investigators

In patients with depressed left ventricular (LV) ejection fraction, preload reserve — LV distension during exercise — was related to clinical status,

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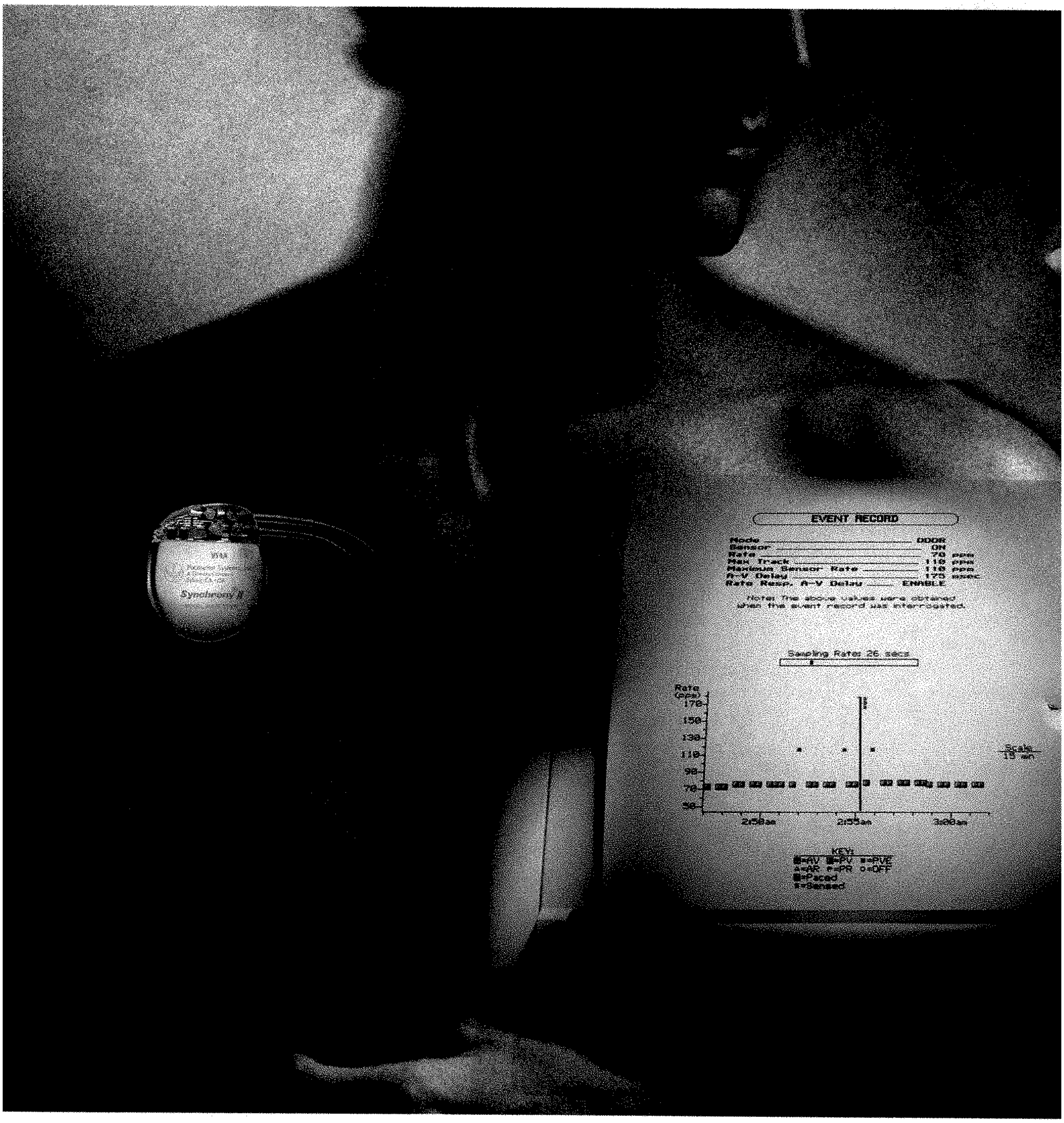

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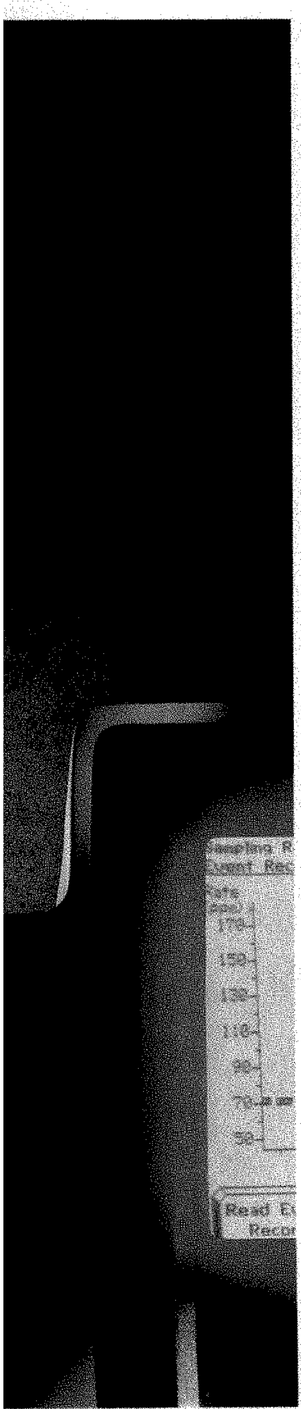

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and the effect of acute angiotensin-converting enzyme inhibition was examined. Compared with 61 asymptomatic patients (group I), 36 symptomatic patients (group II) had higher resting LV end-diastolic and end-systolic volumes, and lower ejection fractions. During exercise, stroke volume increased due to preload recruitment in group I, but not group II, contributing to greater cardiac output response. After administration of intravenous enalapril, end-diastolic volume and cardiac output responses to exercise increased in group II. Thus, in contrast to asymptomatic patients, in patients with symptomatic LV systolic dysfunction, preload reserve is absent, and increases in cardiac output depend on heart rate response. Angiotensin-converting enzyme inhibition may augment preload reserve.

1596

Endothelial Function in Chronic Congestive Heart Failure

Helmut Drexler, Daniel Hayoz, Thomas Münzel, Burckhardt Hornig, Hanjörg Just, Hans R. Brunner, and Robert Zelis

Acetylcholine and N-monomethyl-L-arginine (a specific inhibitor of nitric oxide synthesis from L-arginine) were infused in the brachial artery of healthy volunteer subjects and patients with chronic heart failure (CHF) to examine whether an impaired endothelial function is involved in the limited metabolic peripheral vasodilation of CHF patients. Blood flow response to acetylcholine was blunted in CHF patients compared with that in control subjects. In contrast, the decrease in flow induced by N-monomethyl-L-arginine was enhanced, and the response to nitroglycerin was preserved. Thus, endothelium-dependent dilation of forearm resistance vessels is impaired in CHF, suggesting a reduced stimulated release of nitric oxide. However, the basal release of nitric oxide in a compensatory manner appears to be enhanced.

VALVULAR HEART DISEASE

1602

Long-Term (9 to 33 Months) Echocardiographic Follow-Up After Successful Percutaneous Mitral Commissurotomy

Alessandro Desideri, Olivier Vanderperren, Antonio Serra, Pascal Barraud, Robert Petitclerc, Jacques Lespérance, Ihor Dyrda, Jacques Crépeau, and Raoul Bonan

Late results after successful percutaneous mitral commissurotomy were assessed by prospective clinical and echocardiographic follow-up. Fifty-seven patients were followed for a mean of 19 ± 6 months (range 9 to 33) after the procedure. Mitral valve area (measured by Doppler half-time method) increased from 1.0 ± 0.2 to 2.2 ± 0.5 cm^2 immediately after commissurotomy, and then decreased to 1.9 ± 0.5 cm^2 at follow-up. Restenosis was seen in 21% (12 of 57) of patients, and correlated with age, valve morphology and a suboptimal result. Atrial shunting (small and clinically well-tolerated) was detected in 61% of patients and persisted

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only in 30% at follow-up, influenced by magnitude of shunt, profile of deflated balloon, and mitral valve area achieved. Clinical improvement persisted at long-term follow-up, with 75% of patients gaining ≥1 New York Heart Association functional class.

1607

Methodologic Issues in Clinical Evaluation of Stenosis Severity in Adults Undergoing Aortic or Mitral Balloon Valvuloplasty

Catherine M. Otto, Kathryn B. Davis, David R. Holmes, Jr, William O'Neill, James Ferguson, Thomas M. Bashore, Raoul Bonan, and the principal investigators and echocardiographers of the NHLBI Balloon Valvuloplasty Registry

Invasive valve area and pressure gradient recorded immediately before- and after-aortic (n = 589) or mitral (n = 608) catheter balloon valvuloplasty were compared with Doppler valve area and mean pressure gradients recorded <30 days before and 24 to 72 hours after procedure. The difference between Doppler and invasive valve areas was ≤ 0.5 cm^2 in 98% and <0.2 cm^2 in 87% of patients. For aortic stenosis, variables affecting the valve area difference were cardiac output, aortic regurgitation, heart rate and blood pressure. Mean pressure gradient differences were related to echo quality, blood pressure and mitral regurgitation. For mitral valve area, important variables affecting the differences were mitral regurgitation, interatrial shunt, cardiac output and heart rate. It is concluded that nonsimultaneous studies, differing volume flow measures, and the underlying accuracy of each technique largely account for discrepancies between these methods.

CARDIOMYOPATHY

1617

Predictors of Exercise Benefit After Operative Relief of Left Ventricular Outflow Obstruction by the Myotomy-Myectomy Procedure in Hypertrophic Cardiomyopathy

Jean G. Diodati, William H. Schenke, Myron A. Waclawiw, Charles L. McIntosh, and Richard O. Cannon III

To determine predictors of exercise benefit in patients with hypertrophic cardiomyopathy after operative relief of left ventricular (LV) outflow tract obstruction, 30 patients underwent pre- and postoperative (6 months) catheterization and exercise hemodynamic measurements. The increase in maximal oxygen consumption (VO_2max) during treadmill exercise testing was chosen as an index of exercise benefit. Multivariate analysis of all model variables selected only the preoperative percent predicted VO_2max, and operative reduction in resting LV end-diastolic pressure and resting LV outflow tract gradient as significant predictors of improvement in exercise capacity. Thus, patients with obstructive hypertrophic cardiomyopathy, unsuccessfully treated with medical therapy, are most likely to demonstrate improvement in exercise capacity if preoperative exercise testing demonstrates limited exercise capacity, and if surgery substantially reduces elevated resting LV outflow tract gradients and LV filling pressures.

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1623

Doppler Echocardiographic Assessment of the Pressure Gradient During Bicycle Ergometry in Hypertrophic Cardiomyopathy

Ehud Schwammenthal, Bodo Schwartzkopff, Michael Block, Jan Johns, Benno Lösse, Rolf Engberding, Martin Borggrefe, and Günter Breithardt

The behavior of the pressure gradient during upright bicycle ergometry could be examined in 10 patients with obstructive hypertrophic cardiomyopathy by means of Doppler echocardiography. Additionally, right-sided cardiac catheterization was performed. The pressure gradient increased from 75 ± 24 to 140 ± 42 mm Hg ($p < 0.0005$). Correlation between the resting and exercise gradient was not significant. The increase in stroke volume during exercise, from 90 ± 18 to 95 ± 24 ml ($p < 0.05$), was minimal. Therefore, there was only a moderate increase in systolic flow, from 205 ± 54 to 268 ± 78 ml/s ($p < 0.0005$). Outflow tract resistance increased from 0.38 ± 0.11 to 0.57 ± 0.24 mm Hg · s/ml ($p < 0.01$). Thus, in a selected group of patients with hypertrophic cardiomyopathy, a substantial increase in the pressure gradient during upright bicycle ergometry was demonstrated. Exercise Doppler echocardiography may be valuable to assess the hemodynamic significance of obstruction in individual patients in a physiologic setting.

MISCELLANEOUS

1629

Impairment of Left Ventricular Diastolic Function in Systemic Lupus Erythematosus

Zion Sasson, Yosef Rasooly, Chung Wai Chow, Shane Marshall, and Murray B. Urowitz

Left ventricular (LV) diastolic performance was evaluated with pulsed Doppler echocardiography in 35 patients with systemic lupus erythematosus without overt cardiac disease and in 30 age-matched control subjects; 26 patients were restudied after 7 months. Patients with active disease ($n = 14$) had significantly prolonged isovolumetric relaxation time, reduced ratio of early to late diastolic filling velocity and prolonged mitral pressure halftime when compared with those with inactive disease and with control subjects. Abnormal prolongation of isovolumetric relaxation time (>100 ms) was found to be the most useful marker of diastolic impairment. LV diastolic function did not change appreciably at follow-up, although there was a trend for improvement in those who became inactive. Thus, impaired LV diastolic function is common and persistent in patients with systemic lupus erythematosus, most likely representing myocardial involvement in the lupus process. Further long-term studies are required to determine the clinical and prognostic implications of these findings.

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METHODS

1635
Observations of Coronary Flow Augmentation and Balloon Function During Intraaortic Balloon Counterpulsation Using Transesophageal Echocardiography
Edward S. Katz, Paul A. Tunick, and Itzhak Kronzon

To assess the potential of transesophageal echocardiography in evaluating coronary artery flow augmentation and balloon function during intraaortic balloon pumping, 6 patients were studied. Doppler measurements of left coronary flow were recorded during intermittent balloon inflation. Peak diastolic coronary flow velocity increased during counterpulsation (mean 117%; $p = 0.002$), and coronary flow velocity integral increased by a mean of 87% ($p = 0.003$). Problems associated with balloon pumping discovered by transesophageal echocardiography included incorrect balloon placement, damage to the aortic wall, and balloon mistiming. Transesophageal echocardiography can be used in evaluating intraaortic balloon positioning within the aorta and in monitoring coronary artery flow augmentation during counterpulsation. This relatively noninvasive technique adds another dimension to the evaluation of balloon function and may aid in optimizing the benefits of counterpulsation.

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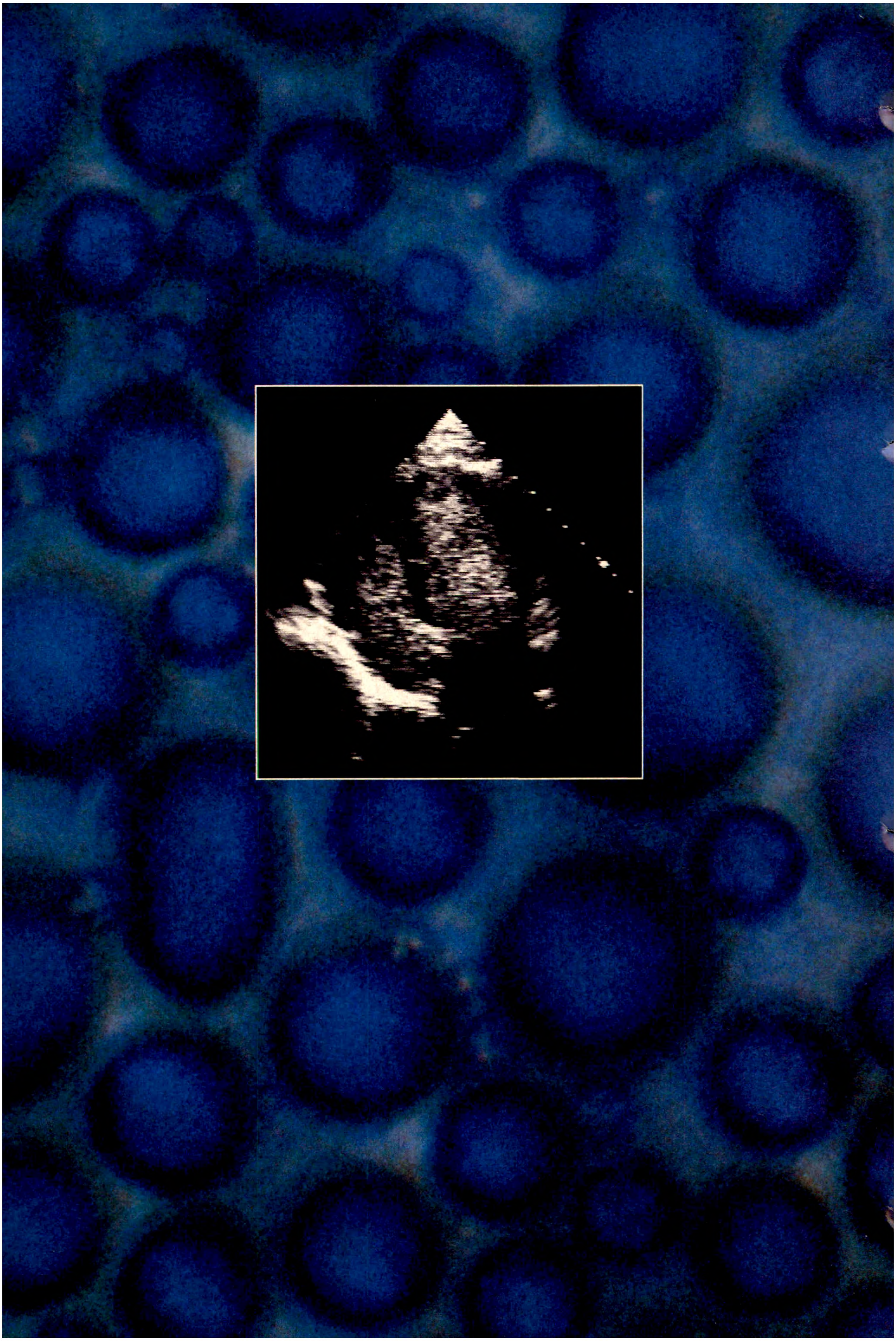

CORONARY ARTERY DISEASE

The American Journal of Cardiology

JUNE 15, 1992, VOL. 69, NO. 19

Mechanism of Exercise-Induced Hypotension in Coronary Artery Disease

Abdulmassih S. Iskandrian, MD, Jeffrey G. Kegel, MD, Joseph Lemlek, DO, Jaekyeong Heo, MD, Virginia Cave, RN, and Basil Iskandrian, BS

Hypotension during exercise testing has been considered a marker of extensive coronary artery disease (CAD) and poor prognosis. The mechanism of hypotension was examined in 25 CAD patients who developed hypotension during treadmill exercise testing (mean decrease in systolic blood pressure [BP] 33 ± 13 mm Hg) (group 1) and was compared with the results of 25 CAD patients who had a normal systolic BP response to exercise (mean increase 53 ± 15 mm Hg) (group 2).

The 2 groups were comparable in age, sex, extent of CAD, previous myocardial infarction, left ventricular ejection fraction, history of hypertension and cardiac medications. Exercise heart rate (121 ± 23 vs 133 ± 25 beats/min; p = not significant [NS]) and duration (6 ± 2 vs 7 ± 3 minutes; p = NS) were comparable. ST-segment depression occurred in 44% of patients in group 1 and in 52% in group 2 (p = NS), and angina during exercise occurred in 60% of both groups. Single-photon emission computed tomographic thallium images were abnormal in 24 patients (96%) in group 1 and in 20 patients (80%) in group 2 (p = NS). Percent thallium abnormality was 19 ± 12% in group 1, and 18 ± 14% in group 2 (p = NS), and the severity of thallium abnormality was 710 ± 510 in group 1, and 510 ± 500 in group 2 (p = NS). Ischemia involving the inferior/posterior segments was seen in 68% of patients in group 1 and in 60% in group 2 (p = NS). Increased lung thallium uptake was seen in 48% of both groups.

Thus, exercise-induced hypotension cannot be explained by the extent of CAD or ischemia; it is probably due to ischemic activation of mechanoreceptors, a mechanism similar to those of other types of neurally mediated hypotension.

(Am J Cardiol 1992;69:1517-1520)

Normal subjects undergoing treadmill exercise testing manifest a decrease in systemic vascular resistance, and increases in cardiac output and systolic blood pressure (BP), with little or no change in diastolic BP. Hypotension during exercise is unusual, but has been reported in some apparently normal subjects, and in patients with coronary artery disease (CAD), aortic stenosis, hypertrophic cardiomyopathy and congestive heart failure.[1-7] In patients with CAD, exercise-induced left ventricular dysfunction (on the basis of either previous infarction or ischemia, or both) has been postulated as the mechanism for exercise-induced hypotension.[7,8] However, most patients with CAD (even those with extensive CAD) have a normal BP response to exercise. Therefore, the precise mechanism of hypotension is unclear. The purpose of this study was to reexamine the mechanism of hypotension during exercise in patients with CAD.

METHODS

Study patients: The study included 25 patients who had exercise-induced hypotension (identified from our computer database of patients undergoing both exercise testing and coronary angiography within 3 months of each other) and CAD (defined as ≥50% diameter stenosis of ≥1 major coronary artery) (group 1). No patient had valvular heart disease, congestive heart failure, recent myocardial infarction, unstable angina, or previous coronary artery bypass surgery or percutaneous transluminal coronary angioplasty. Exercise-induced hypotension was defined as: (1) ≥20 mm Hg decrease in systolic BP from rest to exercise without an initial increase (n = 4); (2) initial increase in systolic BP followed by ≥20 mm Hg decrease during exercise, but exercise systolic BP was still higher than resting systolic BP (n = 12); and (3) initial increase in systolic BP followed by ≥20 mm Hg decrease during exercise, such that exercise systolic BP was lower than baseline upright systolic BP (n = 9). These patients were compared with 25 other patients with CAD who underwent exercise testing and coronary angiography during the same time period, and were matched by age and extent of CAD, but had a normal BP response to exercise (group 2). In group 1, 13 patients were receiving nitrates, 13 were receiving β blockers, and 8 were receiving calcium antagonists; the respective numbers in group 2 were 9, 11 and 8 patients (p = not significant [NS]).

From the Philadelphia Heart Institute, Presbyterian Medical Center, Philadelphia, Pennsylvania. Manuscript received December 11, 1991; revised manuscript received February 19, 1992, and accepted February 20.

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TABLE I Pertinent Data in Patients with Hypotensive Response

Pt.	Age (yr) & Sex	Q-MI	Coronary Artery > 50%	LVEF (%)	METs	Peak HR (beats/min)	Systolic Blood Pressure (mm Hg)			ST Depression	Thallium Results			
							Rest	Maximum	Peak		Abnormal	Ischemia	Extent	Severity
1	69M	0	1	NA	10	120	130	160	140	0	+	+	14	338
2	61M	0	2	82	6	142	170	200	180	0	+	+	17	351
3	73M	0	3	70	2	143	140	170	150	+	+	+	30	1,029
4	48M	0	2	52	10	138	150	170	140	+	+	+	17	556
5	60M	+	2	40	5	134	110	130	90	0	+	+	43	1,823
6	52M	0	2	61	9	130	120	200	160	0	+	+	NA	NA
7	67M	0	3	33	7	145	130	170	140	0	+	+	16	411
8	67F	0	1	81	5	171	120	165	140	0	0	0	1	32
9	52F	+	1	52	4	72	130	110	110	0	+	0	20	475
10	72M	+	3	42	3	98	110	110	80	0	+	0	18	447
11	60M	0	3	82	7	105	150	170	130	+	+	+	NA	NA
12	64M	0	3	70	7	107	130	160	130	0	+	+	13	443
13	38M	0	3	49	13	154	100	150	120	0	+	+	34	1,536
14	75M	+	2*	64	5	125	130	150	130	+	+	+	19	522
15	76M	0	3	NA	6	126	170	190	130	+	+	+	5	104
16	64M	0	2	NA	7	111	120	130	110	+	+	+	15	392
17	49M	0	2	54	3	125	130	150	110	0	+	0	19	586
18	75M	0	1	NA	4	89	130	130	100	0	+	+	10	213
19	69F	0	2	49	6	146	140	190	160	0	+	0	22	1,125
20	68M	0	3*	66	7	111	120	140	110	+	+	+	14	337
21	71M	0	3	NA	4	126	150	170	110	+	+	+	19	470
22	59F	0	1	64	7	118	150	150	110	+	+	+	23	878
23	76M	0	1	68	5	100	160	180	120	+	+	+	38	1,485
24	67M	0	2	NA	7	111	120	160	140	0	+	+	30	1,202
25	62M	0	3*	20	7	80	120	140	100	+	+	+	39	1,484

*Patients 14, 20 and 25 had left main disease.
HR = heart rate; LVEF = left ventricular ejection fraction; NA = not available; Q-MI = Q-wave myocardial infarction; + = present; 0 = absent.

Exercise testing: All patients underwent symptom-limited exercise testing using the Bruce or modified Bruce protocol. Cardiac medications were withheld on the morning of the test. BP was recorded during each minute of the test and during the recovery period. The test was stopped because of excessive fatigue, moderate to severe angina pectoris, ≥2 mm ST depression or when systolic BP decreased lower than the resting systolic BP. Exercise electrocardiograms were interpreted as negative, positive or inconclusive for ischemia as previously described.[9]

Thallium-201 myocardial imaging was performed using single-photon emission computed tomography as previously described from our laboratory.[10] In summary, a dose of 3 mCi of thallium-201 was injected 1 minute before termination of the exercise, and images were obtained within 10 minutes. Delayed images were obtained 4 hours after the initial images, and 20 minutes after the reinjection of 1 mCi of thallium-201. For quantitation of perfusion abnormality, a polar coordinate or bull's-eye map was used. Each patient's profile was compared with the sex-matched normal file, and the abnormality was defined if data points were 2.5 SD below the mean normal limit. The extent of the perfusion abnormality was estimated as the percentage of the total myocardium, and the severity score was derived from the extent and number of SD below the mean normal limit for each point within the abnormal area.

Statistical analysis: Data were presented as mean ± SD when appropriate. Chi-square and 2-tailed Student's *t* test were used. A value <0.05 was considered significant.

RESULTS

Pertinent data of the hypotensive group are listed in Table I and of the normal BP response group in Table II. Age, sex, extent of CAD, left ventricular ejection fraction and presence of previous Q-wave myocardial infarction were similar in both groups. There was history of hypertension in 10 patients in group 1 and in 12 in group 2, and history of diabetes mellitus in 4 in group 1 and in 1 in group 2 (p = NS).

Changes in systolic BP in the 2 groups are shown in Figure 1. There was a 33 ± 13 mm Hg decrease in systolic BP from rest to peak exercise in the hypotensive group, and a 53 ± 15 mm Hg increase in the control group.

Exercise variables in the 2 groups of patients are listed in Tables I and II. Exercise heart rate (121 ± 23 vs 133 ± 25 beats/min; p = NS) and duration (6 ± 2 vs 7 ± 3 minutes; p = NS) were not significantly different; 32% of patients in the hypotensive group, and 36% in the control group achieved ≥85% of maximum predicted heart rate. ST-segment depression and angina during exercise occurred in similar frequencies in both groups.

Thallium studies showed that 24 patients in group 1 (96%), and 20 in group 2 (80%) had abnormal images; reversible defects consistent with ischemia were seen in 80% in group 1 and in 68% in group 2 (p = NS). Ischemia involved the inferoposterior wall in 68% of patients

TABLE II Pertinent Data in Patients with Normal Blood Pressure Response

Pt.	Age (yr) & Sex	Q-MI	Coronary Artery > 50%	LVEF (%)	METs	Peak HR (beats/min)	Systolic Blood Pressure (mm Hg) Rest	Maximum	Peak	ST Depression	Thallium Results Abnormal	Ischemia	Extent	Severity
1	57M	+	2	48	7	129	130	170	170	0	+	+	24	501
2	62M	0	3	64	10	102	130	180	180	0	+	+	33	788
3	69F	0	2	89	3	111	110	150	150	+	0	0	0	0
4	75M	0	1	75	3	74	130	170	170	0	+	+	6	144
5	67M	0	2	60	13	145	120	180	180	+	+	+	16	439
6	62M	0	3	45	7	150	110	150	150	0	+	+	38	1,873
7	65M	0	3	68	10	130	150	210	210	0	0	0	0	0
8	63M	0	3	70	7	103	110	170	170	+	+	+	25	737
9	67M	0	2	80	10	132	110	180	180	+	+	+	6	131
10	68M	0	3*	31	7	148	170	200	200	+	+	+	27	798
11	74M	0	3*	66	6	115	130	200	200	+	+	+	18	385
12	66M	0	1	80	10	148	140	190	190	+	+	+	5	113
13	50M	+	2	75	7	138	150	230	230	+	+	+	15	464
14	68F	0	1	83	7	122	130	200	200	0	0	0	0	0
15	65M	0	3	65	13	155	125	180	180	0	+	+	8	201
16	65F	0	1	NA	7	125	130	170	170	0	0	0	0	0
17	39M	0	3	70	11	124	130	170	170	+	+	+	20	564
18	62M	0	2	91	10	154	110	190	190	0	0	0	0	0
19	64M	0	3	73	4	98	130	160	160	+	+	+	27	606
20	46M	+	1	81	13	175	130	220	220	+	+	+	31	910
21	59M	0	2	54	7	184	110	150	150	+	+	+	13	306
22	68M	+	1	42	10	152	100	170	170	0	+	0	35	1,483
23	56M	0	2	64	3	151	120	190	190	+	+	+	44	1,079
24	64M	0	2	46	4	128	160	200	200	0	+	+	41	1,149
25	61M	0	3*	68	7	123	130	170	170	+	+	+	5	115

*Patients 10, 11 and 25 had left main disease.
Abbreviations as in Table I.

in group 1 and in 60% in group 2 (p = NS). Extent and severity of thallium abnormalities were similar in the 2 groups of patients. There were 7 patients with resting systolic BP ≥150 mm Hg in the hypotensive group; the results were similar when these patients were excluded.

DISCUSSION

The results of this study show that in the presence of comparable extent of CAD and myocardial ischemia, some patients may develop hypotensive response during exercise while others have a normal response. This raises the possibility that an alternative mechanism for hypotension other than the anatomic and functional severity of CAD may be important.

Blood pressure response to exercise: In normal subjects, dynamic exercise results in an increase in systolic BP despite a decrease in systemic vascular resistance. This increase is due to an increase in cardiac output caused by increases in heart rate and stroke volume. The increase in stroke volume is due to left ventricular dilatation and a decrease in end-systolic volume reflecting the contribution of the Frank-Starling mechanism and inotropism.[1,7,11-13]

Most patients with CAD develop ischemia during exercise; however, they have an increase in systolic BP. Even though end-systolic volume increases with exercise, the increases in heart rate and left ventricular dilation are sufficient to augment the cardiac output. These patients may possibly also have a less than normal decrease in systemic vascular resistance.[1,7,11-13] Cardiac output seldom decreases during exercise in CAD patients, despite severe left ventricular dysfunction. Thus, for the BP to decrease there should be a decrease in cardiac output, or a disproportionate decrease in systemic vascular resistance, or both.

Previous studies: The prevalence of hypotension during exercise depends on the definition; approximately 8% of CAD patients undergoing exercise testing have a hypotensive response, and almost 50% of these will have 3-vessel CAD or left main disease.[2,4-8] The risk of death or myocardial infarction is increased in patients with a hypotensive response during exercise if there is

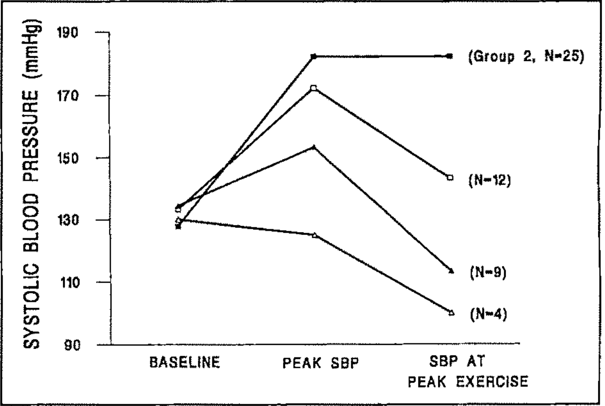

FIGURE 1. Change in systolic blood pressure (SBP) during exercise in patients with hypotensive response (group 1) and normal response (group 2).

evidence of ischemia or left ventricular dysfunction.[4,5] Patients with recent infarction (<3 weeks) do not have the same increased risk as do those with an older infarction. A decrease in systolic BP below the resting value is more important as a risk predictor. In a previous study from our laboratory, patients with hypotension during exercise had prior myocardial infarction, abnormal left ventricular ejection fraction, multivessel CAD and larger thallium abnormalities compared with those with a normal systolic BP response.[2] In that study, we used a ≥10 mm Hg decrease in systolic BP as a criterion for hypotensive response, and planar thallium imaging. In the current study, we used a ≥20 mm Hg decrease in systolic BP, and single-photon emission computed tomography. As in the previous study, most patients with hypotension had multivessel CAD and large thallium abnormality. However, we have shown that other patients with a similar extent of CAD and ischemia have a normal BP response; thus, these factors alone cannot explain the abnormal BP response.

Neurogenic hypotensive response: Neurally mediated hypotension was recently documented as a mechanism of syncope in some normal subjects.[14-18] This reflex involves activation of mechanoreceptors in the myocardium that triggers vagally induced slowing of the heart rate, or a decrease in systemic vascular resistance, or both. This bradycardia/hypotension response (Bezold-Jarisch reflex) has also been implicated as the mechanism of hypotension in patients with aortic stenosis and hypertrophic cardiomyopathy, and in some patients with acute inferior myocardial infarction.[19] Vigorous left ventricular contraction (especially in the presence of reduced end-diastolic volume) has been thought to be the mechanism that initiates this reflex activation. These mechanoreceptors are more predominant in the inferior and posterior segments of the myocardium. Of interest, most of our patients had inferior and posterior ischemic thallium abnormalities. Furthermore, ejection fraction was normal, and heart rate during exercise was slightly lower in the hypotensive response group than in patients with normal BP response. β blockers have been effective in preventing this type of hypotension in some but not all patients.[17] Other patients have responded to disopyramide, a drug that has β-blocking and vagolytic effects.[17] Most of our patients were receiving β-blocker therapy, but in some patients with CAD, β blockers may induce hypotension by blunting the heart rate response. Thus, although this study concurs that a hypotensive response may occur in patients with CAD, and be associated with extensive CAD and a large area of myocardial ischemia, it raises doubt concerning the mechanism of hypotension. It is conceivable that a neurally mediated mechanism due to activation of the mechanoreceptors is also responsible for hypotension in CAD patients.

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Frequency and Predictors of Left Ventricular Segmental Dysfunction in Patients with Recent Rest Angina

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The relation between coronary artery lesion morphology and associated segmental left ventricular (LV) dysfunction in patients with unstable angina is unclear. Fifty-two patients with angina occurring at rest who underwent cardiac catheterization within 3 days of the last episode of pain and had no enzymatic evidence for myocardial necrosis were evaluated. Coronary artery narrowings deemed responsible for the ischemic episodes were analyzed with regard to the artery involved, maximal diameter of the narrowing, presence of thrombus, and complex appearance. Time to catheterization, age, sex and electrocardiographic evidence of ischemia were also noted. Segmental LV dysfunction in the territority supplied by the "culprit lesion" was present in 58% of patients. It occurred significantly more often with lesion location in the left anterior descending coronary artery, and was less frequent with lesions in the left circumflex and ramus coronary arteries. Ischemic electrocardiographic changes were more sensitive in predicting LV dysfunction with culprit lesion location in the left anterior descending or right coronary artery. LV dysfunction could not be predicted by any other parameter analyzed. It is concluded that postischemic LV dysfunction occurs frequently in rest angina, especially when the severest narrowing is in the left anterior descending coronary artery.

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Coronary angiography in patients with unstable angina has demonstrated a higher incidence of intracoronary thrombosis and complex lesion morphology than found in those with stable angina pectoris.[1-5] These morphologic changes in the coronary arteries may provide the substrate for intermittent total or subtotal occlusion, producing the clinical picture of angina at rest with the attendant potential for myocardial depression.[6] However, the frequency of postischemic segmental left ventricular (LV) dysfunction after angina at rest has not been well characterized. We evaluated 52 patients with rest angina who underwent cardiac catheterization within 72 hours of the last episode of chest pain to assess the incidence of segmental LV dysfunction in this setting, and to evaluate whether its occurrence could be predicted by a number of clinical and angiographic variables.

METHODS

Patients: All patients underwent cardiac catheterization for evaluation of chest pain occurring at rest. Data were retrospectively collected for 1987 through 1989 by analyzing patients admitted to the coronary care unit who underwent cardiac catheterization within 3 days of admission for chest pain (n = 27). Patients were included in the study if they had significant coronary artery disease, chest pain at rest, and no enzymatic evidence for myocardial necrosis. From December 1989 through July 1991, patients were prospectively enrolled at the time of catheterization if they fit the study design (n = 35). All patients had to undergo coronary arteriography within 72 hours of the last episode of rest pain. Patients with evidence of myocardial necrosis based on increase in either total creatine kinase or its MB fraction were excluded from the study, as were those with remote myocardial infarction, unless they had a previous cardiac catheterization documenting segmental wall motion abnormalities due to the previous infarction. All patients needed to have coronary anatomy that was amenable to analysis with an identifiable "culprit lesion" and a left ventriculogram that could be interpreted without ambiguity for inclusion in the study. Patients with global hypokinesis and multiple segmental wall motion abnormalities were excluded.

Coronary angiography: Standard coronary angiography in multiple views was performed using the femoral approach. Coronary angiograms were reviewed by 2 independent cardiologists; coronary stenoses were measured with calipers and were graded relative to a normal-appearing adjacent segment in the same vessel.

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TABLE I Clinical Characteristics in 52 Patients with Rest Angina

Parameter	Number
Mean age (yr)	56 ± 12
Men/women	41 (79%)/11 (21%)
Age >70 years	7 (13%)
Time to catheterization (hours) from last episode of rest pain	
<24	26 (50%)
24 to 72	26
Ischemia by electrocardiogram	39 (75%)
Previous coronary bypass	3 (6%)
Previous coronary angioplasty	3
Previous myocardial infarction	3

TABLE II Angiographic Characteristics in 52 Patients with Rest Angina

Abnormal left ventricular wall motion (in area supplied by culprit lesion)	30 (58%)
Lesion severity (luminal diameter reduction)	90 ± 9%
Lesion location	
Left anterior descending	20 (38%)
Right	18 (35%)
Left circumflex/ramus	13 (25%)
Left main	1 (2%)
Filling defect present	11 (21%)
Complex lesion morphology (filling defect, hazy, irregular borders, ulceration)	26 (50%)

Complex lesion morphology was defined as presence of an intraluminal filling defect, haziness, eccentricity, overhanging edges or ulcerated appearance.[2,5] Only 1 coronary stenosis was deemed to be the "culprit lesion" for each patient. In patients with >1 severe stenosis, the culprit lesion was considered to be either the most severe stenosis or the one with complex morphologic characteristics.[7,8] A total occlusion was not considered to be the "culprit lesion."

Left ventricular function: LV angiography was performed using standard techniques in the 30° right anterior oblique view in all patients. If a patient had significant disease involving the circumflex coronary artery, a 60° left anterior oblique ventriculogram was needed for data analysis. All ventriculograms were reviewed by 2 cardiologists for assessment of segmental wall motion abnormalities. Anterior wall motion abnormalities were ascribed to ischemia in the distribution of the left anterior descending coronary artery, and posterior wall motion abnormalities were ascribed to the circumflex; abnormalities in the inferior wall were correlated with right coronary artery ischemia unless the circumflex coronary artery was dominant. Patients were excluded from analysis if LV wall motion was uninterpretable owing to multiple ventricular premature complexes. If the reviewers could not reach agreement concerning segmental wall motion abnormalities due to the subtle nature of the dysfunction, wall motion was considered to be normal.

Electrocardiographic analysis: Electrocardiographic evidence of ischemia was defined as new ST depression or elevation, or new T-wave inversion. Changes were considered to be new if they appeared or developed during hospitalization. If the electrocardiographic changes were present on admission, a prior electrocardiogram was needed for comparison.

Statistical analysis: Statistical analysis was performed with chi-square testing for discrete variables, and a t test for continuous variables. Values are expressed as mean ± SD. A p value <0.05 was considered significant.

RESULTS

Clinical characteristics: The study group included 52 patients (79% men, mean age 56 years, 12% aged >70) (Table I). Half of the patients had catheterization performed within 24 hours of the last episode of rest angina, whereas the other half underwent catheterization from 24 to 72 hours after rest pain. Thirty-nine patients (75%) had electrocardiographic evidence of myocardial ischemia. Two patients underwent previous coronary artery bypass grafting, and 3 had previous coronary angioplasty. Two of the latter patients were thought to have angina based on restenosis of the prior angioplasty site, whereas the other one had a new lesion not previously dilated.

Angiographic characteristics: The vessel responsible for the instability was the left anterior descending in 20 patients (38%), the right coronary artery in 18 (35%), and the circumflex or ramus artery in 13 (25%) (Table II). Only 1 patient was thought to be symptomatic from a severe stenosis involving the left main coronary artery. Average lesion severity (as measured by calipers) was 90 ± 9%. Abnormal segmental LV wall motion occurring in the distribution of the culprit coronary lesion was observed in 30 patients (58%) and ranged from mild to severe hypokinesis, with no akinesis or dyskinesis noted. This involved the anterior distribution in 16 patients (80% of those with culprit lesion in left anterior descending), the inferior in 8 (44% of those with right coronary artery culprit lesions), and the lateral in 5 (38% of those with culprit lesion in circumflex) ($p < 0.05$).

Predictors of segmental left ventricular dysfunction: The following lesion and patient characteristics were analyzed as potential predictors of abnormal segmental LV systolic function: age and sex, time from instability to catheterization, electrocardiographic evidence of ischemia, lesion morphology and severity, and artery involved (Table III). Patients undergoing diagnostic catheterization on the second or third day after the last episode of rest angina were found to be as likely to have segmental wall motion abnormalities as were those undergoing catheterization within 24 hours of rest pain. Likewise, electrocardiographic evidence of ischemia did not predict segmental LV dysfueven if these lesion characteristics were combined with the descriptors of diminished distal flow (Thrombolysis in Myocardial Infarction grade I–II). Abnormal regional wall motion was not more likely to be found in women or the eldenction. Fifty percent of patients had complex lesions, but this finding was not predictive of abnormal segmental wall motion in the distribution of the vessel responsible for the instability. Segmental dysfunction could not be predicted rly (aged >70 years). Average lesion severity was 88.5% in patients with segmental LV dysfunction, and 92.8% in those with normal regional wall motion (p = not significant).

When patients were analyzed by lesion location, abnormal segmental LV function was more frequently associated with left anterior descending lesions. There was a significant negative association with abnormal segmental wall motion in patients with the culprit lesion in the left circumflex or ramus coronary artery. The 1 patient with severe stenosis and thrombus involving the left main coronary artery had normal LV function.

Ability of the electrocardiogram to predict wall motion: The presence of anterior ischemic electrocardiographic changes and a lesion in the left anterior descending artery had an 81% sensitivity in predicting abnormal segmental LV motion, but a specificity of only 25%. Likewise, the combination of inferior ischemic changes by electrocardiogram, and a lesion in a dominant right coronary artery had a 78% sensitivity in predicting regional myocardial dysfunction, but a specificity of 22%. Lateral electrocardiographic changes and a lesion in the circumflex or ramus artery had a sensitivity of only 60%, and a specificity of 38% for abnormal segmental wall motion.

DISCUSSION

In this study, segmental LV dysfunction was present in a significant proportion of patients with rest angina (58%). This postischemic LV dysfunction was as frequent in patients studied early (<24 hours) as in those studied late (24 to 72 hours) after the last episode of chest pain. Although new electrocardiographic evidence of ischemia occurred in 75% of patients, it was not predictive of a resting wall motion abnormality. Likewise, lesion severity, intracoronary thrombus and complex lesion morphology were not predictive of segmental LV dysfunction. However, patients with a culprit lesion in the left anterior descending coronary artery were more likely to have segmental LV dysfunction. This may be due to the large amount of myocardium supplied by the left anterior descending artery and to the fact that severe lesions often involve the proximal third of this vessel. However, a nondominant circumflex coronary artery often supplies relatively less myocardium than do the other 2 major vessels, and these patients were more likely to have normal wall motion than was the group as a whole.

These data are in agreement with those of a previous study that noted a significant association between anterior wall dysfunction in patients with unstable angina and the presence of a critical left anterior descending stenosis.[9] This myocardial depression was not seen in patients without negative T waves on electrocardiogram and was normalized with improved flow after successful angioplasty. In the present study, a culprit lesion involving the left anterior descending artery was very sensitive (81%) but poorly specific in predicting segmental wall dysfunction on left ventriculography.

The segmental LV dysfunction observed in our patients with rest angina was ischemia-related and presumably reversible. "Myocardial stunning" is a reversible form of contractile dysfunction that can occur after restoration of coronary blood flow following a relatively brief period of coronary occlusion.[10] This dysfunction is reversible within several days to a week and assumes transient interruption of coronary flow in its pathogenesis. Alternatively, the term "myocardial hibernation" has been used to describe a state of sustained abnormal contraction due to chronic underperfusion in the setting of coronary artery disease.[11] In a recent review, both myocardial stunning and hibernation were described as possible outcomes in cases of diminished myocardial flow (perfusion-contraction matching).[12] Both experimental and clinical evidence were cited for the phenomena of acute (stunning) and sustained low-flow (short-term hibernation) perfusion-contraction matching. The clinical picture of unstable angina pectoris was thought to most closely resemble the example of short-term hibernation. The potential for recovery of contractility in these patients has already been demonstrated by surgical revascularization[13,14] and coronary angioplasty[15-17] both in the acute and chronic phases of ischemic dysfunction. In a recent study[18] improvement in regional and global LV contractility was demonstrated immediately after balloon angioplasty. Early catheterization and intervention appears to be appropriate in patients with rest angina to detect and reverse the frequent segmental LV dysfunction.

TABLE III Incidence of Abnormal Left Ventricular Wall Motion Relative to Various Parameters

	Abnormal LV Motion	Normal LV Motion	p Value
Age (yr)	54 ± 11	58 ± 14	0.19
Catheterization <24 hours	15	11	1.00
Catheterization 24 to 72 hours	16	10	1.00
Ischemia by electrocardiogram	23	16	1.00
Lesion severity	88 ± 9%	93 ± 7%	0.09
Presence of thrombus	6	5	0.98
Complex lesion (thrombus, hazy, irregular)	15	11	0.78
Age >70 years	3	5	0.39
Lesion location			
Left anterior descending	16	4	0.02
Right	9	9	0.60
Circumflex/ramus	5	8	0.02
Left main	0	1	—

LV = left ventricular.

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Acute and Long-Term Effects on Myocardial Ischemia of Intermittent and Continuous Transdermal Nitrate Therapy in Stable Angina

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The aim of this study was to compare the efficacy and safety of continuous and intermittent transdermal nitrate therapy using ambulatory electrocardiographic (Holter) monitoring. Eighty-five patients with stable angina pectoris and positive exercise test results participated during their concomitant antiischemic medication in a randomized open trial lasting 12 weeks. After a 3-week run-in period with continuous therapy (10 mg/24 hours), patients were randomized to either continuous- or intermittent-therapy groups. In the intermittent-therapy group the patients removed their patch at night (the mean patch-off period was 10 hours). Forty-eight-hour Holter monitoring was performed in each patient after randomization, and again after 2 and 12 weeks. Eighteen patients withdrew, 9 in each group.

A total of 11,194 hours of electrocardiography were recorded and 607 ischemic episodes were detected, of which 79% were asymptomatic and 95% appeared during daytime. The number of ischemic episodes per 48 hours with intermittent therapy was 3.1 ± 0.7 (mean ± SEM) after randomization, 1.8 ± 0.4 at 2 weeks and 2.0 ± 0.6 at 12 weeks. With continuous therapy the respective numbers were 3.8 ± 1.1, 3.5 ± 0.9 and 4.2 ± 1.2. The differences were not statistically significant because a large number of patients (30%) had no ischemic episodes on Holter recording. However, when examining 47 patients with episodes during the study, the number of episodes was significantly reduced in the intermittent-therapy group ($p < 0.05$ at 12 weeks). The changes in asymptomatic and symptomatic episodes were concordant. No changes and differences between the treatment groups were seen in nighttime episodes.

Results suggest that intermittent transdermal nitrate therapy is superior to continuous therapy in reducing ischemic episodes. The nighttime nitrate-free interval does not lead to increased ischemia in patients with concomitant antiischemic medication.

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The purpose of this study was to compare the efficacy of continuous and intermittent nitrate therapy using ambulatory electrocardiographic (Holter) monitoring in patients with stable angina pectoris during their concomitant antiischemic medication. Special emphasis was focused on the safety of intermittent therapy. Several previous studies have shown that continuous transdermal nitroglycerin therapy is a potent inducer of nitrate tolerance thus leading to reduction of its antianginal effects.[1,2] However, numerous studies have demonstrated that the beneficial actions of nitrates during exercise can be maintained with a nitrate-free interval,[3–10] but limited information is available about myocardial ischemia during these nitrate-free intervals.[6,11,12] Holter monitoring has previously been widely used to detect and quantify myocardial ischemia in patients with proven coronary artery disease.[13–17] The ischemic findings on Holter monitoring have been shown to have a predictive value especially in unstable angina[18–20] but also in stable coronary artery disease.[21] Holter monitoring could enable the assessment of whether there is a rebound increase in the number of ischemic episodes during the nitrate-free period. If no rebound exists, then improving efficacy by intermittent therapy is not associated with an increase in ischemia.

It has previously been shown that transdermal nitrate therapy has a beneficial effect on the quality of life in patients with angina pectoris.[22] However, there are no studies that have explored the relation between quality of life and ischemic episodes during Holter monitoring. Therefore an evaluation of the quality of life was included in this study to detect any link between the frequency of ischemic episodes and quality of life.

METHODS

Patients: Patients from 6 Health Centers from the province of North Karelia, Finland (Joensuu, Lieksa, Kitee, Ilomantsi, Outokumpu and Nurmes) participated in a multicenter, between-patient, blindly randomized, open-label study of continuous versus intermittent transdermal nitrate therapy. Two-hundred-fifty patients identified as having stable angina pectoris of ≥3 months' duration and who had a positive exercise test result were invited to participate; 143 patients entered

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the screening phase. Ninety-five patients fulfilled the inclusion criteria: cooperative male patients with a stable typical angina pectoris currently receiving long-acting oral or transdermal nitrate treatment and responding to sublingual oral nitrate tablets, with a positive exercise test result and 24-hour Holter monitoring of good quality.

The exclusion criteria were unstable angina or angina at rest, myocardial infarction within 3 months of enrollment, coronary angioplasty or coronary bypass surgery in the previous 3 months, left bundle branch block, left ventricular hypertrophy, baseline ST depression >1 mm, digitalis therapy, or any other disease or clinical abnormality that could affect the reliability of Holter analysis or preclude patient participation in the trial.

Ten patients decided not to enter the study after the run-in period, 9 because of unwanted effects and 1 because of previously planned coronary bypass surgery. Eighty-five patients were included in the study. Thirty-seven of them had a previous myocardial infarction and 14 had angiographically documented coronary artery disease (11 of the patients with angiographically documented disease also had previous myocardial infarction).

Trial design: During the screening phase patients underwent exercise testing and 24-hour Holter monitoring during their previous medication (Figure 1). After a 3-week run-in period with continuous transdermal nitrate therapy, patients were randomly and blindly allocated to either intermittent or continuous transdermal nitrate therapy (10 mg/24 hours) and continued on their assigned treatment for the duration of the study (12 weeks). After randomization (beginning of treatment period), patients underwent 48-hour Holter monitoring (acute phase, starting in the morning before the first nitrate-free night in the intermittent-therapy group) followed by another 48-hour Holter monitoring after 2 and 12 weeks (early and late chronic phases). Patients receiving intermittent therapy were asked to remove the patch just before going to bed or ≥8 hours before getting up. The exact time of patch application and removal was recorded in a personal diary. Patients were requested to keep an accurate and detailed diary containing information on their day- and nighttime physical activities, anginal attacks and sublingual nitrate consumption.

Exercise test: All patients performed an upright bicycle ergometer exercise test once during the screening phase. The Mason-Likar modification of standard 12-channel electrocardiography was recorded (Case-12, Marquette Electronics Inc.), and blood pressure and heart rate were measured every minute during the exercise. The first work load was 30 W, and was increased by 15 W increments at 1-minute intervals. The test was continued until extreme fatigue, 90% of the predicted maximal heart rate was reached, or other standard criteria for termination of exercise test were fulfilled. During the 10-minute recovery period all test parameters were recorded. The test was considered positive if an ST depression of ≥1 mm measured 80 ms after the J point was observed in any precordial lead. In case of mild resting baseline ST depression (≤1 mm) an additive ST-segment depression of ≥1 mm was accepted as evidence of ischemia.

Holter monitoring: All recordings were obtained with amplitude modulated (Marquette Electronics Inc. series 8000) tape recorders. Bipolar leads were attached with the exploring electrodes at positions V_5 and V_3. Special care was taken to prepare the skin and to secure electrodes firmly to avoid motion artifacts. Each patient was instructed to perform his usual daily activities and to maintain a detailed written diary with emphasis on any symptoms during the recording. All recording periods began between 8 and 10 A.M. and 8 minutes of calibration was recorded at the beginning of each tape. Arrhythmias and noise artifacts were excluded from the analysis. All tapes were interpreted with an interactive digital Holter analysis system (Marquette Laser Holter XP, Marquette Electronics Inc.) by the same physician without knowledge of study medication regimens. A random sample of 25 tapes were audited (blindly reanalyzed) using Cardiodata Prodigy System.

Criteria for determination of significant myocardial ischemia were ≥1 mm ST-segment depression measured 60 ms after the J point lasting ≥1 minute. In the case of baseline resting ST depression (on the electro-

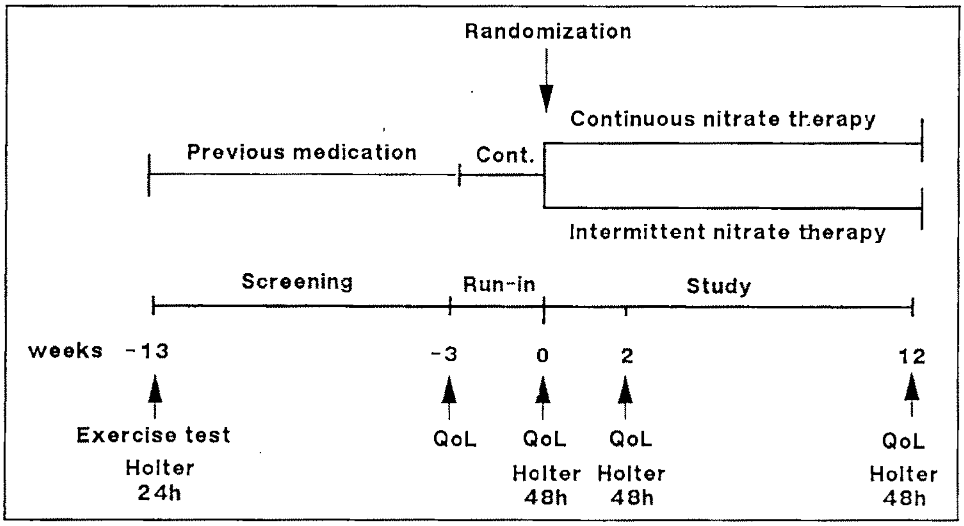

FIGURE 1. The study protocol. Cont. = continuous nitrate therapy in all patients; QoL = quality of life.

TABLE I Patient Characteristics by Treatment Group

	Patients Including Withdrawals		Patients Excluding Withdrawals	
	Cont. (n = 41)	Int. (n = 44)	Cont. (n = 32)	Int. (n = 35)
Age (yr ± SEM)	56 (1)	58 (1)	56 (1)	57 (1)
Duration of angina pectoris (yr)	3.5 (0.6)	5.3 (0.6)	3.6 (0.6)	5.7 (1.0)
Mean no. of angina pectoris attacks during last 14 days	12.0 (2.9)	11.6 (2.2)	11.6 (3.0)	7.5 (1.6)
Mean duration of exercise test (min)	6.9 (0.4)	6.7 (0.3)	6.8 (0.4)	7.0 (0.3)
Mean duration to 1 mm ST depression in exercise test (min)	5.4 (0.4)	5.7 (0.3)	5.8 (0.4)	5.8 (0.3)
Mean no. of ischemic episodes on Holter monitoring during run-in phase (24 hours)	1.7 (0.6)	1.3 (0.6)	1.7 (0.5)	1.3 (0.3)
Mean total quality of life score	114 (4)	114 (3)	116 (4)	119 (4)
No. of pts. previously taking transdermal nitrates (%)	3 (7%)	4 (9%)	3 (9%)	4 (11%)
No. of pts. taking β blockers (%)	32 (78%)	30 (68%)	24 (75%)	24 (69%)
No. of pts. taking calcium antagonists (%)	21 (51%)	25 (57%)	16 (50%)	18 (51%)
No. of pts. with headache (%)	8 (20%)	11 (25%)	7 (22%)	9 (26%)

Values are mean ± SEM.
Cont. = continuous nitrate-therapy group; Int. = intermittent nitrate-therapy group; Patients Excluding Withdrawals = all differences between treatment groups not significant.

cardiogram at rest and on the Holter ST trend), an additional ST depression ≥1.5 mm was accepted as ischemic (patients with ≥1 mm of baseline ST depression on the ST trend were excluded from the study during screening phase). The time interval between separate episodes had to be ≥2 minutes. The baseline was calculated automatically utilizing the average value of the surrounding ST measurements during 1 hour before and after the episode and the level was also visually verified from the ST trend. The heart rate at the beginning of each episode was recorded. All episodes were also visually confirmed from the electrocardiography printout. Episodes of ST elevation and T-wave changes were not counted because these changes occur frequently in normal subjects during Holter monitoring.[23]

The number of episodes and the total duration of ischemia during each phase were calculated. Respective calculations for symptomatic, asymptomatic, daytime and nighttime episodes were also performed. Daytime in the intermittent-therapy group was considered to begin when the patient applied the patch in the morning and nighttime when he removed the patch. For patients receiving continuous nitrate therapy, daytime was considered to start when the patch was changed. Because the mean duration of daytime was 14 hours (14.1 ± 1.4 hours) in the intermittent-therapy group, this duration was also applied to patients receiving continuous therapy as the duration of daytime.

Quality of life questionnaires: A 24-item quality of life questionnaire designed for use in clinical trials in patients with angina pectoris was self-administered.[24] Apart from giving an overall score, the 24 items provide 3 dimensions depicting health-related symptoms (8 items), the impact of disease and day-to-day functioning (8 items), and psychological well-being (8 items). Additionally a 5-item sleep questionnaire was also completed by the patients.[25] Patients filled in their answers to the quality of life questionnaires at home before the next visit.

Statistical methods: Baseline characteristics used to assess homogeneity of the 2 treatment groups were: (1) age, duration of angina pectoris, duration of exercise test, time to ischemic ST depression during exercise test (ischemic threshold and total quality of life score) tested using analysis of variance; and (2) number of angina pectoris attacks and number of ischemic episodes on Holter monitoring (24 hours) tested using the Wilcoxon test.

Formal statistical tests were performed on Holter monitoring data (both the number of episodes and their duration) for all patients, and separately for only those with at least 1 episode during the study, and at the acute, early and late chronic phases. Change from the acute phase at both the early and late chronic phases was also examined. The Wilcoxon test was used in all cases. The number of attacks (from the patient diary) and number of sublingual nitrates used at the acute, early and late chronic phases were tested with the Wilcoxon test.

The Wilcoxon test was preferred for analysis after investigation of the normality of the parameters under test. Correlation coefficients presented are the Spear-

TABLE II Mean Number of Episodes and Mean Duration of Ischemia in Both Treatment Groups

	Treatment Group			
	Continuous (n = 32)		Intermittent (n = 35)	
All Patients	Mean	SEM	Mean	SEM
Acute phase (48 hours)				
All episodes: no.	3.8	(1.1)	3.1	(0.7)
Duration (min)	26	(8)	24	(5)
Episodes ≥ 1: no. of patients	17		20	
Mean heart rate at onset of episode	105	(3)	106	(3)
Peak (negative) ST depression	−3.1	(0.3)	−2.8	(0.3)
Early chronic phase (2 weeks) (48 hours)				
All episodes: no.	3.5	(0.9)	1.8	(0.4)
Duration (min)	29	(11)	11	(4)
Episodes ≥ 1: no. of patients	15		20	
Mean heart rate at onset of episode	102	(4)	101	(4)
Peak (negative) ST depression	−2.4	(0.2)	−2.1	(0.2)
Late chronic phase (12 weeks) (48 hours)				
All episodes: no.	4.2	(1.2)	2.0	(0.6)
Duration (min)	28	(9)	15	(5)
Episodes ≥ 1: no. of patients	18		14	
Mean heart rate at onset of episode	95	(4)	94	(4)
Peak (negative) ST depression	−2.5	(0.2)	−3.1	(0.4)
	(n = 22)*		(n = 25)*	
Patients with Episodes During the Study	Mean	SEM	Mean	SEM
Acute phase (48 hours)				
All episodes: no.	5.5	(1.5)	4.3	(0.8)
Duration (min)	38	(11)	33	(7)
Early chronic phase (2 weeks) (48 hours)				
All episodes: no.	5.2	(1.2)	2.5	(0.5)
Duration (min)	43	(16)	16	(5)
Late chronic phase (12 weeks) (48 hours)				
All episodes: no.	6.1	(1.6)†	2.8	(0.8)
Duration (min)	41	(12)	21	(6)

*Patients without episodes throughout the study are removed.
†Significant difference between the groups ($p < 0.05$).
Duration = duration of ischemia; no. = number of ischemic episodes per 48 hours.

man rank correlation coefficients. All tests were performed using procedures from SAS, and the 5% level of statistical significance was used. Although in most instances nonparametric testing has been performed, results are presented in terms of mean ± standard error.

RESULTS

Baseline data: A total of 85 patients were randomized: 41 to the continuous- and 44 to the intermittent transdermal nitrate–therapy group. Patient characteristics are listed in Table I. There was no imbalance between the 2 treatment groups.

Withdrawals: A total of 18 patients withdrew from the study, 9 in each treatment group. The comparability of the remaining 67 patients was confirmed before starting analysis (Table I). Four patients withdrew because of skin irritation (3 receiving continuous and 1 intermittent therapy), 3 because of chest pain (1 receiving continuous and 2 intermittent therapy), 3 because of bypass surgery planned before the study (1 receiving continuous and 2 intermittent therapy), 4 because they misunderstood the protocol (1 receiving continuous and 3 intermittent therapy), 1 because he felt better and discontinued his transdermal nitrate therapy (continuous therapy) and 1 because he decided to use the patch only intermittently.

There was one sudden death in the continuous-therapy group; this patient had completed his acute and early chronic phase Holter recordings, which showed no ischemic episodes. One patient randomized to the intermittent group withdrew from the study because of unstable angina after 4 weeks. This patient had several daytime but no nighttime ischemic episodes in the acute and 2-week recordings.

Transdermal nitrate therapy, β blocker and calcium antagonists: All patients except 1 in the intermittent-therapy group used one 10 mg/24 hour (20 cm^2) patch per day. Six patients had no concomitant antiischemic medication. Twenty-seven patients (14 receiving continuous and 13 intermittent therapy) received β-blocker therapy, 21 patients (10 received continuous and 11 intermittent therapy) were given both β blockers and calcium antagonists and 13 patients (6 received continuous and 7 intermittent therapy) were given only calcium antagonists (Table I). Six patients changed their dose of β blocker or calcium antagonist: 2 patients (taking intermittent therapy) discontinued β-blocker therapy and began therapy with a calcium antagonist, 2 patients reduced the dosage of the β blocker (one in each group), 2 patients taking intermittent therapy discontinued therapy with a calcium antagonist. No patient increased the dose of β blockers.

CLINICAL FINDINGS

Number of anginal attacks and sublingual nitrate consumption: The mean number of anginal attacks during the screening phase was 11.6 ± 3.0 in the continuous-therapy group and 7.5 ± 1.6 in the intermittent-therapy group (all patients were taking continuous therapy). During the first 2 weeks after randomization it was 10.0 ± 2.5 and during the last 2 weeks 6.7 ± 1.7 in the continuous-therapy group. In the intermittent-therapy group the numbers were respectively 6.4 ± 2.0 and 4.4 ± 1.1 (changes during time and differences between groups were not significant [NS]). The respective numbers in the sublingual nitrate consumption were 7.4 ± 1.8, 6.8 ± 1.6 and 5.2 ± 1.3 in the continuous-therapy group and 5.2 ± 1.6, 5.0 ± 1.9 and 4.1 ± 1.4 in the intermittent-therapy group (changes during time and differences between groups, NS).

Holter monitoring: One patient missed 2 recordings at 2 weeks. The analyzable duration of an additional 2 tapes from separate patients was only 17 hours because of noise artifacts. All other patients had complete recording periods, and this produced a total of 467 accepted 24-hour tapes and 11,194 hours of electrocardiographic recordings. Fourteen patients were found to have mild (<1 mm) baseline ST depression and the relative criteria were used. The mean number of episodes per 48 hours in each patient was 3.0 ± 4.8 (mean ± SD, range 0 to 32) and the mean duration of the episodes 22 ± 42 minutes (mean ± SD, range 1 to 308 minutes). A total of 607 ischemic episodes were detected, 480 of which (79%) were asymptomatic and 575 episodes (95%) appeared during daytime.

NUMBER AND DURATION OF ISCHEMIC EPISODES DURING EACH PHASE: The mean number of ischemic episodes during screening phase 24-hour Holter monitoring and during the first 48 hours after randomization (the acute phase) was not different in the continuous- and intermittent-therapy groups (1.7 ± 0.6 and 1.3 ± 0.6 during screening phase and 3.8 ± 1.1 and 3.1 ± 0.7 during acute phase, respectively, p = NS, Tables I and II). During chronic phases a clear trend for a decrease in the number of episodes was seen in the intermittent-therapy group (Figure 2). In contrast, there was no

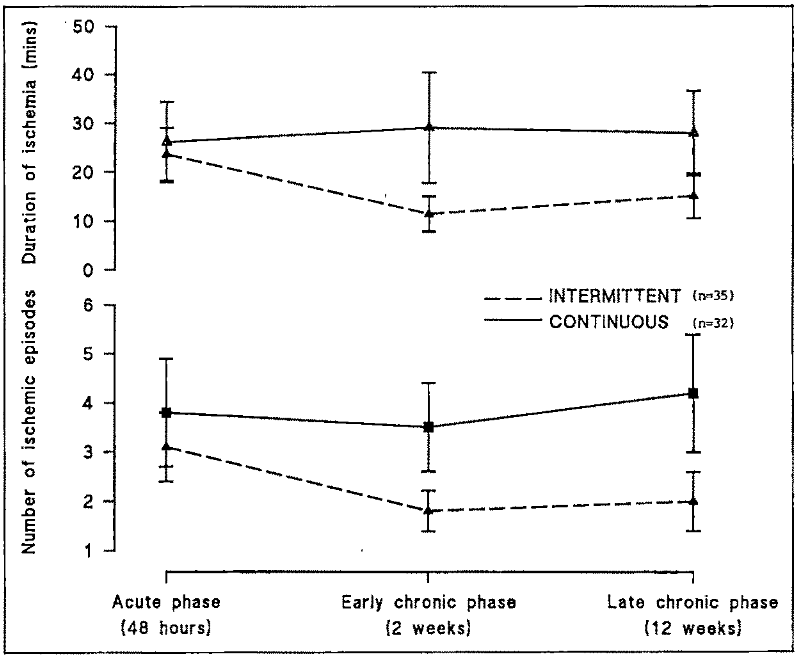

FIGURE 2. Mean number of ischemic episodes and duration of ischemia in both treatment groups in each phase (all patients). All data are mean ± SEM.

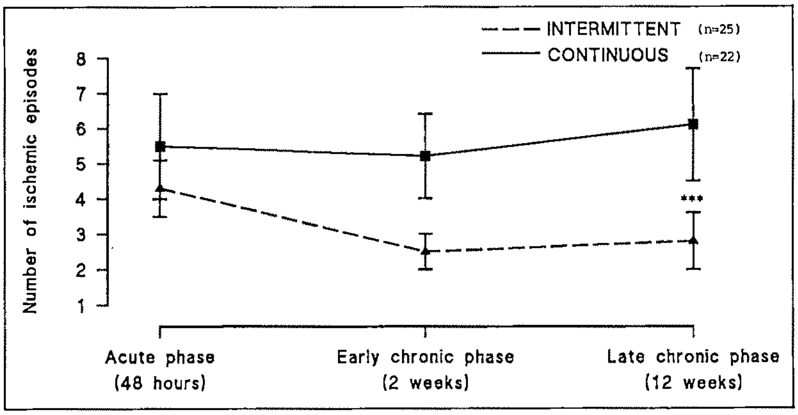

FIGURE 3. Mean number of ischemic episodes in both treatment groups in each phase (patients without episodes throughout the study were removed). All data are mean ± SEM. *** p <0.05 in the Wilcoxon test.

TABLE III Daytime and Nighttime Episodes and Symptomatic and Asymptomatic Episodes in Both Treatment Groups

	Treatment Group							
	Continuous (n = 32)				Intermittent (n = 35)			
	Day		Night		Day		Night	
	Mean	SEM	Mean	SEM	Mean	Sem	Mean	SEM
Acute phase (48 hours)								
All episodes: no.	3.6	(1.1)	0.2	(0.2)	2.9	(0.6)	0.2	(0.1)
Duration	24	(8)	2	(1)	23	(6)	1	(1)
No. of patients with episodes	17		6		20		3	
Early chronic phase (2 wks) (48 hours)								
All episodes: no.	3.5	(0.9)	0		1.6	(0.4)	0.2	(0.1)
Duration	29	(11)	0		11	(4)	0.5	(0.4)
No. of patients with episodes	15		0		18		4	
Late chronic phase (12 wks) (48 hours)								
All episodes: no.	4.0	(1.1)	0.2	(0.1)	1.8	(0.5)	0.2	(0.1)
Duration	27	(9)	1	(1)	14	(4)	1	(1)
No. of patients with episodes	18		2		14		5	
	Symptomatic		Asymptomatic		Symptomatic		Asymptomatic	
	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM
Acute phase (48 hours)								
All episodes: no.	0.9	(0.4)	2.9	(0.9)	0.8	(0.2)	2.2	(0.6)
Duration	9	(4)	17	(6)	10	(3)	13	(5)
No. of patients with episodes	8		15		13		16	
Early chronic phase (2 wks) (48 hours)								
All episodes: no.	0.8	(0.4)*	2.7	(1.1)	0.2	(0.1)	1.6	(0.4)
Duration	11	(5)*	19	(7)	2	(1)	10	(3)
No. of patients with episodes	8		15		6		17	
Late chronic phase (12 wks) (48 hours)								
All episodes: no.	0.8	(0.5)	3.4	(1.0)	0.2	(0.1)	1.8	(0.6)
Duration	5	(2)	23	(8)	4	(2)	11	(4)*
No. of patients with episodes	7		18		4		12	

*Significant difference between groups.
Four episodes not classified as either symptomatic or asymptomatic have been excluded from this table.
Abbreviations as in Table II.

change in the continuous-therapy group. Despite the apparently clear differences in the treatment groups, the nonparametric statistical tests applied did not reveal significant treatment group differences. The bimodality of the distribution of results (approximately 50% of patients at each phase had no ischemic episodes and 30% of patients had no episodes throughout the study) confounded the differences in statistical testing. However, when excluding patients with no ischemic events during Holter monitoring throughout the study (Table II, Figure 3), the number of episodes was reduced significantly in the intermittent-therapy group when compared with the continuous-therapy group ($p < 0.05$ at 12 weeks). The results for the duration of ischemia were in agreement with the changes in the number of episodes (Table II, Figure 2). The results for symptomatic and asymptomatic episodes were also in accordance with the total number of episodes (Table III).

NIGHT- AND DAYTIME ISCHEMIA: There was no evidence of "rebound" ischemia in the intermittent-therapy group compared with continuous-therapy group throughout the study (Table III). Only 5% (127 episodes) appeared at night during Holter recordings. Examination of individual patients' Holter monitoring data showed only 7 patients with ischemia during the first night of the acute phase (4 patients with continuous and 3 patients with intermittent therapy) and the mean duration of nighttime ischemia in these patients was 10.2 minutes in the continuous- and 9.2 minutes in the intermittent-therapy group. The number of patients having nighttime ischemia during the study was 7 in the continuous- and 9 in the intermittent-therapy group. The mean number of nighttime episodes per patient in these groups were 1.9 and 2.0, respectively, and the mean duration of ischemia 11.1 and 10.1 minutes. All patients with nighttime episodes also had daytime episodes, and all except 2 patients also had a relatively high (6 to 56 episodes) number of daytime episodes. The 6 patients who received only the nitrate as antianginal therapy showed no evidence of increased nocturnal angina. Also no difference was found in day- or nighttime physical activities between the treatment groups.

Adverse effects: The number of patients complaining of headache, and its severity, was comparable in both groups during the course of the study.

Quality of life: Table IV lists quality of life scores (including subdimensions and sleep). In both groups patients tended to improve in the early chronic phase and return to their original (acute phase) value in the late chronic phase. A significant correlation between the

TABLE IV Mean Quality of Life Score in Both Treatment Groups

	2 Weeks Before Entry				First 2 Weeks				Last 2 Weeks			
	Continuous		Intermittent		Continuous		Intermittent		Continuous		Intermittent	
	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM
Total	116	(4)	119	(4)	118	(4)	121	(4)	116	(4)	119	(4)
Well-being	41	(1)	42	(1)	42	(1)	42	(1)	41	(1)	41	(1)
Impact of disease	38	(2)	39	(2)	38	(2)	40	(2)	38	(2)	40	(2)
Symptoms	37	(1)	38	(1)	37	(1)	38	(1)	37	(1)	38	(1)
Sleep	24	(1)	24	(1)	25	(1)	24	(1)	24	(1)	24	(1)

number of ischemic episodes and total quality of life score was revealed at both randomization (r = −0.32, acute phase) and the late chronic phase (r = −0.30) for symptomatic episodes. The sleep questionnaire score was correlated only with nighttime ischemic episodes at the late chronic phase (r = −0.25). All other correlations were nonsignificant.

DISCUSSION

The results of this study indicate that in patients with concomitant antiischemic medication, rebound angina is not a problem during intermittent transdermal nitrate therapy with an overnight nitrate-free period. In 2 previous trials[6,11] a small number of patients have been reported to have increased nocturnal angina with intermittent therapy, whereas in 2 other studies[4,7] no such events occurred. In this study 6 patients received only the nitrate as antianginal therapy, and no increase in nighttime ischemia was found. There was also no increase in the consumption of short-acting nitrates. In other patients the presence of concomitant medication may have played a role in preventing rebound ischemia during the night.

We studied the efficacy of intermittent and continuous nitrate therapy in patients who were mostly taking either a β blocker or a calcium antagonist, thus resembling the situation in clinical practice. Previous studies with oral and transdermal nitrates have been performed either in patients receiving other antianginal medication[6,7] or after withdrawal of concomitant drugs.[4] In industrialized countries, >75% of patients with angina are treated with ≥2 antianginal medications; the figure for patients with severe angina is probably much higher. Based on the results of this study it seems that intermittent transdermal nitrate therapy has an additive antiischemic effect over concomitant medication and is superior to continuous therapy. However, we cannot tell if continuous therapy is beneficial in preventing ischemia because there was no placebo treatment group or period in this study. Our results are in accordance with previous studies in which antianginal effects were primarily measured by exercise testing,[6] although in the present study the use of Holter monitoring provides an additional dimension for direct examination of antiischemic effects during daily life. In previous studies the time to 1 mm ST depression during exercise has been shown to increase after the first application of nitrates[4,7,26-28] and, conversely, dosing regimens with 8- to 12-hour nitrate free intervals have demonstrated the preservation of nitrate antianginal effects.[6,7,27]

In this blindly randomized trial, an open comparison was chosen in order to compare continuous and intermittent transdermal nitrate therapy under conditions of normal daily life. Although an open comparison, all Holter recordings were analyzed blindly. A placebo treatment period or separate placebo patient group was not included in the protocol because we believe it to be ethically inappropriate to stop nitrate treatment in patients with angina pectoris for a 3-month study period.

Quality of life measurements were used as a secondary parameter to examine patient acceptability of intermittent therapy (i.e., to examine the presence or absence of subjective adversity). The clinical validity of the quality of life findings is supported by the correlation between symptomatic events and quality of life. A previous trial has shown improved quality of life in patients receiving long-term continuous transdermal nitrate therapy.[13] In the present study intermittent therapy was shown not to have any adverse effect on the quality of life or on sleep.

Study limitations: A common problem in studies of myocardial ischemia using Holter monitoring is the great variability of ischemic episodes between and within patients over time. Therefore, to show any changes in ischemia, a large number of patients and a long recording period are needed. In addition, in this study the patients without episodes during Holter monitoring present a problem with regard to statistical analysis. It is well known that ischemic episodes do not always occur during normal life in all patients with coronary artery disease. Based on the results of this study we are not able to ascertain if continuous therapy is beneficial in preventing ischemia because no placebo treatment period was included. Furthermore, we cannot tell if nitrate tolerance developed during continuous therapy because no comparable 48-hour Holter monitoring was performed during the screening phase. Despite these limitations, in this trial the absence of any rebound angina on ambulatory electrocardiographic monitoring during intermittent nitrate patch therapy, combined with patient acceptability, is reassuring.

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Immediate and Follow-up Results of the Conservative Coronary Angioplasty Strategy for Unstable Angina Pectoris

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To assess the results of a conservative coronary angioplasty strategy in unstable angina pectoris, the records of 1,421 consecutive patients without previous myocardial infarction undergoing a first percutaneous transluminal coronary angioplasty (PTCA) between 1986 and 1990 were reviewed. Of these patients, 631 had unstable and 790 had stable angina pectoris. Only after an intense effort to medically control symptoms, the unstable patients underwent PTCA at an average of 15.4 days (range 1 to 76) after hospital admission. Primary clinical success was achieved in 91.7% of patients with unstable and in 94.4% of those with stable angina pectoris (p = not significant). In-hospital mortality rates were 0.3 and 0.1%, respectively (p = not significant). Nonfatal in-hospital event rates for acute myocardial infarction, cerebrovascular accident and coronary bypass surgery were only slightly higher in patients with unstable angina pectoris; however, the difference from the stable group was significant when all events were combined (9 vs 5.9%; p <0.04). During 6-month follow-up, no significant difference in adverse events was found between the groups. The respective rates for the unstable and stable groups were 0.4 and 0.2% for death, 5.5 and 5.1% for major nonfatal events, and 17.7 and 20.1% for repeat PTCA. These results suggest that use of a conservative PTCA strategy in the treatment of patients with unstable angina pectoris results in favorable and similar immediate and 6-month outcomes compared with those in patients with stable angina pectoris.

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It is generally accepted that unstable angina pectoris results from an acute intracoronary event, including rupture, fissuring or intramural hemorrhage of an atherosclerotic plaque followed by platelet activation and thrombus formation, with or without superimposed coronary artery spasm.[1] In the early 1980s, immediate coronary recanalization was considered to be the most appropriate treatment for this occlusive event. However, early percutaneous transluminal coronary angioplasty (PTCA) resulted in a lower primary success rate, higher complication rate and a less favorable 6-month outcome than did delayed PTCA or PTCA for stable angina pectoris.[2-8] These observations and the fact that symptoms often stabilize with appropriate medical treatment[9] raised the issue of the optimal timing of PTCA for unstable angina pectoris. The present study assesses the in-hospital and 6-month follow-up results of the conservative approach, in which patients with unstable angina pectoris are first medically stabilized as much as possible before undergoing PTCA. These results were compared with those obtained in patients with stable angina pectoris treated during the same study period.

METHODS

Study groups and treatment policies: Between October 1986 and October 1990, after exclusion of PTCA procedures for restenosis, 2,337 consecutive patients underwent a first PTCA at our center. Of these patients, 916 (39%) had a previous myocardial infarction and were excluded from further analysis. Thus, the population comprised 1,421 patients, of whom 631 presented with unstable and 790 with stable angina pectoris. Patients with unstable angina pectoris were subdivided in 2 groups; those without history of ischemic symptoms (n = 389), and those with an exacerbation of chronic stable angina pectoris (n = 242).

For unstable symptoms PTCA was only performed after intense efforts to stabilize patients with intravenous nitrates and oral calcium antagonists, as well as β-blocking agents. Furthermore, intravenous heparin and oral aspirin were routinely administered. In unstable as well as stable patients, the PTCA procedure, postprocedural in-hospital management and follow-up outpatient visits were standard, and were previously described in this journal.[10]

Definitions: Patients were considered to have unstable angina pectoris when the referring indication was the occurrence of spontaneous anginal attacks at rest, irrespective of whether they were of recent onset or an exacerbation of previously stable symptoms. Thus, all

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TABLE I Patient Baseline Characteristics

	Unstable Patients (n = 631)	Stable Patients (n = 790)	p Value
Age (yr)	60 ± 9	59 ± 9	NS
Men/women	2.6/1	3.1/1	NS
Smoking (%)			
Current	261 (41)	266 (34)	0.01
Previous	191 (30)	265 (34)	
Systemic arterial hypertension* (%)	201 (32)	276 (35)	NS
Diabetes mellitus* (%)	71 (11)	58 (7)	0.02
Average serum cholesterol (mg/dl)	244 ± 53	254 ± 52	NS
ST-segment changes (%)	271 (43)	142 (18)	0.001
Narrowings attempted per patient	1.3	1.3	NS
Coronary arteries narrowed			
1	429 (68)	522 (66)	NS
2	158 (25)	200 (25)	
3	27 (4)	37 (5)	
Prior bypass grafting	17 (3)	31 (4)	

*Defined as necessitating treatment.
NS = not significant.

TABLE II Angiographic Characteristics of Attempted Lesions (%)

	Unstable Angina (n = 837)	Stable Angina (n = 1,042)	p Value
Arteries attempted			
Left anterior descending	373 (45)	490 (47)	NS
Left circumflex	229 (27)	282 (27)	
Right	227 (27)	257 (24.5)	
Left main	—	5 (0.5)	
Venous graft	8 (1)	7 (1)	
Multiple stenoses within same balloon length	28 (3)	29 (3)	NS
Length >2× normal arterial diameter	162 (20)	189 (18)	NS
Stenosis located in bend >45°	33 (4)	50 (5)	NS
Thrombus in stenosis	32 (4)	19 (2)	0.01
Calcified plaques	115 (14)	141 (13)	NS
Eccentric lumens	397 (47)	552 (53)	0.03
Total occlusions	38 (5)	53 (5)	NS

NS = not significant.

these patients were (according to the Braunwald classification system)[11] in severity class II or III.

Coronary lesions were visually estimated in 2 perpendicular views and expressed as the percent diameter reduction from the nearest "normal" arterial segment. Lesions with ≥50% diameter reduction were considered significant and targeted for dilatation if the vessel supplied a sizable area of viable myocardium. Primary lesion success at PTCA was defined as a final reduction in luminal narrowing by ≥20% to a residual narrowing of <50%. Primary clinical success was defined as successful dilatation of the culprit lesion without the occurrence of death, myocardial infarction or emergency coronary bypass surgery during hospitalization. Intimal dissection was defined as an intimal flap with a double-lumen contour extending beyond the site of the lesion. Acute rethrombosis was defined as an intracoronary filling defect that compromised the vessel patency by >50%. Repeat PTCA was defined as an attempt to reopen the previously dilated artery after clinical or electrocardiographic evidence, or both, of acute occlusion had occurred outside the catheterization laboratory. Thus, reintroduction of the balloon catheter for filling defects observed at the end of the initial PTCA procedure was not included in this definition. Cardiac enzymes were determined by clinical indication, and myocardial infarction was defined by a typical increase of >2 times the upper normal limits of creatine kinase or by an MB fraction >4%, or both. Untoward events were defined as death, cerebrovascular accident, coronary artery surgery, repeat PTCA and myocardial infarction. At control angiography, restenosis was defined as >50% coronary narrowing at the site of prior dilatation.

Statistical analysis: All relevant clinical and angiographic data were prospectively entered in a computer-based registry, details of which were reported elsewhere.[12] All data were recorded at the beginning and end of hospital stay, as well as during 6-month follow-up. Data are expressed as mean ± SD. Intergroup analysis was performed using SAS, a commercially available computer program. A p value <0.05 was considered significant.

RESULTS

Baseline characteristics: More unstable angina pectoris patients were current smokers (p = 0.01), and had diabetes mellitus (p = 0.02) and persistent ischemic ST-segment changes (p <0.001) than did stable patients (Table I). The mean time interval between hospital admission and performance of PTCA was 15.4 days (range 1 to 76) in unstable patients. PTCA was performed within the first week after admission in only 14% of patients. The mean number of lesions targeted for PTCA was 1.3/patient in each group. The angiographic characteristics of these lesions are listed in Table II. As expected, more intraluminal thrombi were observed in unstable than in stable patients (p = 0.01). Thrombi were more frequently seen in patients with a clinical history of <1 week (9%) than in those with a history of >1 week but <1 month (2.7%; p = 0.001).

In-hospital results: The primary lesion success rates (including dilatation of chronic occlusions) were 91.2% in the unstable group, and 89.6% in the stable group (p = not significant [NS]). Stenosis severity decreased from 87.8 ± 9.3% to 28.6 ± 22% in the unstable group and from 88.1 ± 9.5% to 29.4 ± 23.3% in the stable group (p = NS).

Immediately after inflations, angiographic evidence of thrombus formation prompting reintroduction of the balloon catheter was seen in 5.9% of unstable and in 4.4% of stable patients (p = NS). However, during the period between final removal of the guiding catheter and the patient's return to the ward, acute reocclusion occurred more frequently in the unstable patients (6.7 vs 3%; p = 0.001). The incidence of later in-hospital reocclusion was exactly the same in both groups (1.6%). The percentages of patients with rethrombotic episodes was 13.1% in the unstable group, and 8.3% in the stable group (p = 0.003). As expected, these differences resulted in more acute repeat PTCAs in unstable than in stable patients (5.4 vs 3.2%; $p = 0.05$). This initial strategy was effective in 88% of stable and in 76% of unstable patients.

These procedural problems also resulted in a number of major in-hospital adverse events (Table III). Death, myocardial infarction, emergency coronary surgery and cerebrovascular accidents were slightly more frequent in the unstable group, but the differences in these individual events were not significant. However, when all these complications were combined, the total number of events (57 [9%] in unstable vs 47 [5.9%] in stable patients) was significantly different ($p = 0.03$). At hospital discharge, similar results for primary clinical success rate (91.7 vs 94.4%) and for complete revascularisation (66.2 vs 61.9%) were obtained for the unstable and stable patients, respectively. No difference in the incidence of major events was observed when unstable patients with and without history of stable symptoms were compared. In the subgroup needing PTCA within the first week after admission, only a slight excess in major in-hospital events was observed compared with that in unstable patients treated later (11 vs 8.7%; p = NS).

Follow-up results: Follow-up was completed at a mean of 7.1 ± 5.7 months. During this period, 29% of the unstable group ($n = 601$) and 33% of the stable group ($n = 766$) underwent clinically indicated, repeat coronary angiography; the respective indications were recurrent chest pain (25.6 and 27.3%; p = NS), silent ischemia (2.8 and 5.2%; $p = 0.04$) and nonfatal myocardial infarction (1 and 0.5%; p = NS). Restenosis was found in 89% of unstable and in 91% of stable patients (p = NS). Major adverse follow-up events are listed in Table IV. There was only 1 cardiac and 1 noncardiac death in each group, and differences in the rates of myocardial infarction, coronary bypass surgery and repeat PTCA were not significant. Subdivision of the unstable group into patients with and without prior stable ischemic symptoms revealed no significant differences in these major complications.

DISCUSSION

The results of this study show that in patients with unstable angina pectoris, a strategy of delayed PTCA is associated with an acceptably low in-hospital complication rate of 9% and with a primary clinical success rate of 91.7%. These results were obtained in 631 consecutive patients treated during the years 1986 to 1990 after exclusion of those with restenotic lesions (generally accepted to be associated with less procedural problems than are primary lesions). Conversely, the low death rate of 0.3% may have been favorably influenced by the exclusion of patients with a previous myocardial infarction who have less functional reserve if complications occur during PTCA of a noninfarct-related artery. Our minimum follow-up period of 6 months (the risk period for restenosis) was characterized by a low rate of major cardiac events (death 0.2%, myocardial infarction 1% and coronary bypass surgery 4.5%). These in-hospital and 6-month follow-up results were obtained in patients who presented with chest pain at rest (Braunwald severity class II and III) and appeared to be largely independent of the duration of ischemic symptoms of coronary artery disease. Significantly, 86% of patients with unstable angina pectoris could be stabilized medically during hospital stay. This observation is in complete accordance with a recent hallmark study that reported gratifying short-term results achieved with current conservative medical treatment.[9]

TABLE III Number of Major In-Hospital Events (%)

	Unstable Patients (n = 631)	Stable Patients (n = 790)	p Value
Death*	2 (0.3)	1 (0.1)	NS
Myocardial infarction	23 (3.6)	22 (2.8)	NS
Bypass surgery	30 (4.7)	24 (3.0)	NS
Cerebrovascular accident	2 (0.3)	0	NS
All	57 (9.0)	47 (5.9)	<0.04

*All deaths are postoperative.
NS = not significant.

TABLE IV Number of Six-Month Adverse Follow-Up Events (%)

	Unstable Patients (n = 601)	Stable Patients (n = 766)	p Value
Death			
Cardiac	1 (0.2)	1 (0.1)	NS
Noncardiac	1 (0.2)	1 (0.1)	NS
Myocardial infarction	6 (1.0)	4 (0.5)	NS
Bypass surgery	27 (4.5)	35 (4.6)	NS
Repeat PTCA	106 (17.7)	154 (20.1)	NS
All	141 (23.5)	195 (25.5)	NS

NS = not significant; PTCA = percutaneous transluminal coronary angioplasty.

The use as a control group of 790 consecutive patients with stable angina pectoris without previous myocardial infarction who also underwent a first PTCA at our center during the same study period highlights the efficacy of the delayed PTCA strategy in patients with unstable angina pectoris. Indeed, the primary clinical success rate in the unstable group was only slightly lower and the in-hospital event rates slightly higher than those in the stable group. A significant difference became apparent only when all in-hospital events were combined. It is unlikely that these small differences in acute outcome were directly affected by baseline clinical characteristics such as smoking habits and diabetes, which were more frequent in unstable patients. The very recent and detailed report from the M-Heart study[13] demonstrated that such clinical characteristics do not affect the immediate success rate that in contrast is clearly influenced by lesion characteristics, such as the presence of a thrombus. Because of the delayed PTCA strategy, it was predictable that the incidence of thrombi would be relatively low, but it was still more frequent in unstable than in stable patients.

At least 3 recent studies compared the efficacy of PTCA in patients with unstable and stable angina pectoris.[6–8] The conclusion of these investigations was that

PTCA performed early after onset of symptoms has a markedly increased risk of acute complications and major in-hospital cardiac events in unstable patients. Our results also show some increased risk in the unstable compared with that in the stable group, but the risk is much less striking than was previously reported. These differences can be explained (at least in part) by differing treatment strategies. First, all previous studies refer to a time period (1980 to 1985) when the remarkable efficacy of an initial strategy of repeat PTCA for acute vessel closure was not fully appreciated. This strategy was used in 5.3% of our patients with unstable angina pectoris and in 3.1% of those with stable angina pectoris, which contrasts sharply with the negligible rate (<1%) reported by Kamp et al[6] and Rupprecht et al.[8] Second, in the present study, a delayed interventional strategy was used, as reflected by the low incidence (3.8%) of intracoronary thrombus formation observed in the unstable group. The angiographic presence of an intracoronary thrombus in patients with unstable angina pectoris is a time-related phenomenon, and has been reported to vary from 1%, when 3 months have elapsed between the acute event and angiography, to 57% in patients who had angiography during a spontaneous ongoing attack.[14,15] This angiographic feature is known to be associated with acute vessel closure during and immediately after the procedure.[16] Conceivably, the strategy of watchful waiting provides a partial explanation for lower in-hospital rates of acute myocardial infarction and for the need for emergency bypass surgery. The present findings are supported by a recent study of Myler et al,[7] which found that an aggressive PTCA approach (within 1 to 2 weeks of onset of anginal symptoms) is associated with a lower success rate and higher complication rate than is a delayed strategy. By delaying PTCA and instituting prolonged antithrombotic therapy with heparin and aspirin, one allows time for platelet activity and fibrinopeptide A-levels to diminish.[17,18]

At 6-month follow-up, the rate of major adverse events in patients with initial unstable angina pectoris was 5.9%, which is very similar to that observed in those with stable angina pectoris. Most notable were the very low rates of death (0.4%) and myocardial infarction (1%), although crossover to surgery occurred in 4.5% of patients. These results are in accordance with those of Myler et al,[7] but are different from those of Kamp et al[6] and Rupprecht et al[8] who found a higher incidence of major events (including coronary surgery) in patients with unstable angina pectoris at 6-month and 1-year follow-ups, respectively. We believe that these differences can largely be explained by a different policy of repeat PTCA for recurrent clinical problems. During a 3-year follow-up, Myler et al[7] used repeat PTCA in approximately 30% of their total patient group, which is in accordance with our 19% rate during the first 6 months. In contrast, for a similar 6-month period, Kamp et al[6] reported repeat PTCA in only 7% of patients, whereas Rupprecht et al[8] reported 18.8% during the first year of follow-up. Thus, these observations suggest that when symptomatic or silent ischemia recurs, an aggressive approach of repeat PTCA may limit the number of major adverse follow-up events.

Clinical implications: The results of this study suggest that in patients with unstable angina pectoris, a strategy of delaying PTCA will result in a reduced rate of major in-hospital complications. On the basis of our observations, it appears advisable that every effort should be made to stabilize symptoms in these patients before using PTCA. Furthermore, when in-hospital complications or (during 6-month follow-up) recurrent clinical problems occur, an aggressive strategy of repeat PTCA appears to be rewarding. It is significant that these gratifying results were obtained during a study period when no new technologies specifically addressing the problem of acute rethrombosis were introduced. However, very recently our experience (as well as that of other investigators) with the use of the autoperfusion catheter and balloon-expandable stent has been very encouraging.[19–22] Accordingly, further primary clinical successes can be expected when PTCA is performed in patients with unstable as well as stable anginal symptoms.

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Echocardiographic Algorithms for Admission and Predischarge Prediction of Mortality in Acute Myocardial Infarction

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To develop improved prognostic algorithms for routine bedside use in acute myocardial infarction (AMI), the prognostic value concerning 2- and 12-month mortality of an early (within 72 hours after AMI) resting echocardiogram was defined in 201 consecutive patients. The relation between (1) the clinical variables (age, sex, prior and repeat AMI, arrhythmias, cardiac arrest, early [<72 hours after AMI] and late heart failure, early and maximal in-hospital Killip class, and maximal creatine kinase-MB isoenzyme), (2) early myocardial performance by echocardiography, and (3) mortality was characterized by Kaplan-Meier survival curves and receiver-operating characteristic curves based on Cox regression model. Only age and clinical heart failure in terms of the maximal in-hospital Killip class had independent predictive value of death ($p < 0.05$) when an early echocardiographic estimate of left ventricular ejection fraction (LVEF) was included in the multivariate statistical models. The following 2 optimized algorithms for admission and predischarge calculation of risk of mortality at 2 and 12 months were developed based on the Cox model, using combinations of age, maximal Killip class and early echocardiographic LVEF: mortality at 2 months $= 1 - \exp - [0.051 \times \exp[0.044 \times (\text{age} - 60) - (0.117 \times (\text{LVEF} - 40))]]$; and mortality at 1 year $= 1 - \exp - [0.101 \times \exp[0.408 \times (\text{maxKillip} - 1) - (0.061 \times (\text{LVEF} - 40))]]$. Discriminative power for prediction of mortality of the predischarge algorithm in an independent population of 195 patients 5 days after AMI compared favorably with that obtained in the original population, confirming the validity of the proposed method of prognostication.

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Echocardiography is the most readily available imaging method for bedside definition of risk after acute myocardial infarction (AMI).[1–3] With use of multivariate statistics, echocardiographic left ventricular wall motion index was shown to be the best prognostic predictor for defining early (in-hospital) and late (1-year) mortality compared with historic, clinical and biochemical variables.[4,5] Both visual inspection and wall motion analysis of the left ventricle by echocardiography allow rapid bedside estimation of left ventricular ejection fraction (LVEF), which is a more generally accepted and used parameter for the evaluation of left ventricular global function than are wall motion (score) indexes.[6,7] In the past, these indexes were derived and calculated in a number of ways, limiting widespread uniform use, although recently proposed criteria may change this in the future.[8] The prognostic value and limitations of clinical signs of heart failure in AMI were studied in series of patients of various selection in relation to radionuclide LVEF obtained early or at discharge.[9–11] Less information is available on the prognostic role of clinical heart failure in relation to an early echocardiographic estimate of LVEF. This study defines the prognostic value of early and late clinical signs of heart failure (Killip class) as prognostic markers of 2- and 12-month mortality relative to an early echocardiographic estimate of LVEF, and identifies the most predictive combination of postadmittance and predischarge clinical and echocardiographic variables for the development of easily used admission and predischarge prognostic algorithms after AMI.

METHODS

Patients: INCLUSION: The study group comprised a prospective series of 201 consecutive, unselected patients (145 men [median age 60 years, range 38 to 89] and 56 women [median age 66 years, range 35 to 90]) with creatine kinase-MB–documented AMI.[3] All patients were studied before the introduction of thrombolytic therapy in Denmark. Treatment with β blockade and angiotensin-converting enzyme inhibitors was only used in a few cases on specific indication. No patient underwent coronary angioplasty or bypass surgery during the period of observation. All patients were monitored electrocardiographically throughout the hospital stay and remained in the coronary care unit until discharge (median 14 days after AMI).

FOLLOW-UP: All patients were followed up after 1 year. In-hospital mortality was 22 of 201 patients (10%), 2-month mortality was 31 of 201 (15%), and 1-year mortality was 52 of 201 (26%).

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EXCLUSION: In all, 57 patients with a final diagnosis of AMI during the period of study were not included, because of death before echocardiographic examination (n = 26), admittance >72 hours after the onset of pain (n = 12), doubtful initial diagnosis (n = 11), or concurrent valvular or myopathic disease (n = 8). No patient was excluded owing to poor quality of the echocardiographic study.[3]

Clinical variables: The following clinical variables previously shown to be the most predictive were prospectively recorded [12]: (1) historic: sex, age and number of prior AMIs; and (2) clinical observations: congestive heart failure, reinfarction, asystole, ventricular fibrillation, ventricular tachycardia/extrasystoles (if needing treatment), supraventricular tachycardia and nodal rhythm. Early heart failure and Killip class (at time of first echocardiographic examination), maximal Killip class during hospital stay, and maximal creatine kinase-MB value were also recorded.[13,14]

DEFINITION OF CLINICAL CRITERIA AND VARIABLES: *Heart failure:* Bilateral rales at auscultation, dyspnea or ortopnea, displaced apex beat, presence of an S_3 gallop or radiographic signs of pulmonary congestion were considered signs of heart failure. Neck vein distention, hepatomegaly or edema were interpreted as signs of (right) heart failure. Only signs that prompted the clinician to change (i.e., institute or increase) treatment were accepted as an expression of heart failure. Killip class was defined according to previously published criteria (class 1: no signs of heart failure; class 2: basal bilateral rales; class 3: basal rales over the lower two thirds of lungs [pulmonary edema]; and class 4: cardiogenic shock [systolic blood pressure <80 mm Hg for ≥30 minutes, accompanied by oliguria and clinical signs of shock]). Early Killip class was recorded at the time of echocardiography (within 72 hours after AMI). Maximal Killip class was defined as the highest class observed during admittance.

Asystole: absence of QRS-activity for ≥10 seconds. Asystole as a terminal phenomenon as part of end-stage pulmonary edema, cardiogenic shock or pulmonary embolism did not qualify as such.

Ventricular tachycardia was diagnosed when >3 subsequent ventricular premature beats with frequency >100 beats/min were observed.

Ventricular fibrillation was diagnosed when the electrocardiogram showed absence of QRS complexes and T waves, and presence of symmetric low-amplitude baseline undulations, with variation in both amplitude and periodicity lasting >10 seconds.

Supraventricular tachycardia: >10 successive supraventricular ectopic beats, with frequency >100 beats/min.

Nodal rhythm: regular QRS rhythm without P waves, with frequency <100 beats/min, and QRS duration <0.12 second.

Number of acute myocardial infarctions: number of historic and present clinical episodes of electrocardiographically or enzymatically confirmed, or both, AMIs.

Reinfarction: distinct new clinical episodes of AMI during hospital stay separated in time and by normal creatine kinase-MB values.

Maximal creatine kinase-MB values: Blood samples for the analysis of creatine kinase-MB isoenzymes were obtained on admittance and once daily until normal values were observed.[14] New samples were obtained when reinfarction or infarct extension was suspected.

Echocardiography: Echocardiographic examination was performed, as previously described, at the bedside in the coronary care unit, with the patient in the supine or left lateral position. The examination was performed ≤72 hours after AMI. Cardiac imaging through parasternal longitudinal, cross-sectional (mitral and papillary muscle level), apical 4-chamber and longitudinal views was supplemented by subxiphoid longitudinal and cross-sectional views when feasible.[3] Endocardial wall motion and myocardial thickening were subjectively analyzed within the frame of a 9-segment model.[1] The motion of individual segments was scored as follows: normal motion: +2; hypokinesia: +1; akinesia: 0; paradoxical motion: −1; and hyperkinesia: +3. No correction was made for aneurysmatic segments. Each segment was seen in 2 or 3 projections, and the scores of a particular segment were averaged, resulting in 9 score values.[3] The mean of the 9 score values constituted the wall motion index. The Wall motion index was multiplied by 30 to obtain an estimate of LVEF. This method of estimating LVEF was originally adopted based on experience obtained in a study that used blinded comparison of wall motion index with radionuclide angiographic LVEF in 62 patients examined in the second week after AMI (r = 0.84, SEE 8; unpublished results). The linear relation between wall motion index and LVEF was later confirmed prospectively in an independent study.[7] Patients with LVEF ≥40 (wall motion index >1.3) were allocated to the low-risk group, whereas those with LVEF <40 (wall motion index ≤1.3) were classified as high-risk patients, based on previous experience.[3,7,15]

Statistical analysis: Descriptive statistics were used to characterize quantitative and qualitative data. Nonparametric statistics (Kruskall Wallis) or the chi-square test were used to identify statistical significance, when appropriate. Kaplan-Meier survival curves were used to display the time relation between mortality, estimated LVEF by echocardiography, and clinical variables.[16] Age was dichotomized at a cut-off point of ≥65 years, creatine kinase-MB at the predefined point of best separation at ≥100, and early LVEF <40, representing the break point between high- and low-risk subsets of an unselected population with AMI.[3,15] Statistically significant differences of mortality between the survival curves were evaluated by the log-rank test. Cox regression model for hazards was used to calculate the prognostic value of an early echocardiographic LVEF concerning mortality at 2 and 12 months compared with that of clinical variables.[17] Based on Cox proportional hazards model, receiver-operating characteristic curves were constructed to display the degree of overlap between the distributions of survivors and nonsurvivors for clinical variables individually or combined.[18] With use of the Cox model, admission and predischarge prognostic algorithms were derived, comprising the variables most predictive of mortality.

Table I Clinical Variables According to Survival Status One Year After Acute Myocardial Infarction

Clinical Variables	Survivors (n = 149)	Nonsurvivors (n = 52)	p Value*
Sex (women/men)	36/113	20/32	<0.05
Age (yr) (median [range])	61.2 (35–83)	66.3 (43–90)	<0.005
AMI number (1/2/3/4)	109/31/8/1	40/7/2/3	NS
Reinfarction†	7	1	NS
Asystole†	1	2	NS
Atrial fibrillation†	12	8	NS
Supraventricular tachycardia†	1	0	NS
Ventricular premature complexes†	6	3	NS
Ventricular fibrillation†	11	6	NS
Early heart failure	39	33	<0.0001
Late heart failure	58	43	<0.0001
Early Killip class (1/2/3/4) (n)	110/32/3/4	19/22/3/8	<0.0001
Maximal Killip class (1/2/3/4) (n)	91/40/9/9	9/18/2/23	<0.0001
Maximal CKMB (median [range])	158 (10–1,492)	193 (19–1,524)	NS
Early echocardiographic LVEF (median [range])	41 (15–72)	28 (9–54)	<0.0001

*Kruskall Wallis test (univariate comparison).
†Present within the first 5 days after AMI.
AMI = acute myocardial infarction; CKMB = creatine kinase-MB; LVEF = left ventricular ejection fraction; NS = not significant.

RESULTS

Descriptive clinical data in 201 unselected patients with AMI appear in Table I (dichotomized in survivors and nonsurvivors at 1 year). Significant statistical differences by univariate analysis were indicated. In the group of survivors, 39 of 149 (26%) had early (<72 hours) signs of clinical heart failure, whereas 58 (40%) had signs of heart failure at some point during the hospital stay ($p < 0.05$); the corresponding numbers in the group of nonsurvivors were 33 of 52 (63%), and 43 (83%) ($p < 0.05$), respectively. Early Killip classes 3 and 4 were observed in 7 survivors (5%) and 11 nonsurvivors (21%) ($p < 0.001$), whereas maximal Killip classes 3 and 4 were observed in 18 survivors (12%) and 25 nonsurvivors (48%) ($p < 0.0001$). As expected, age was higher and LVEF lower in nonsurvivors, but prior and repeat AMI, and the various arrhythmias did not contribute to the separation of groups in this study. Early LVEF and maximal in-hospital Killip class showed the best discrimination between survivors and nonsurvivors.

In Figure 1, Kaplan-Meier survival curves are seen for early and maximal Killip class combined with LVEF dichotomized at $\geq/<40$ (low vs high risk). It appears that LVEF and Killip class were complementary for risk stratification (i.e., patients with low Killip class and LVEF had similar mortality to that of those with high Killip class and LVEF; $p > 0.05$).

In Tables II and III, echocardiographic LVEF and the most predictive clinical variables are weighted for postadmittance and predischarge prognostic value concerning mortality at 2 and 12 months using the log-likelihood test. The most predictive single parameters concerning 2-month mortality were age and LVEF on admittance (Table II), and concerning 1-year mortality were maximal in-hospital Killip class on discharge, and LVEF (Table III).

Based on Cox regression model, the following algorithm was derived for postadmittance calculation of risk of mortality at 2 months, using the age of the patient, and an early echocardiographic estimate of LVEF: 1 −

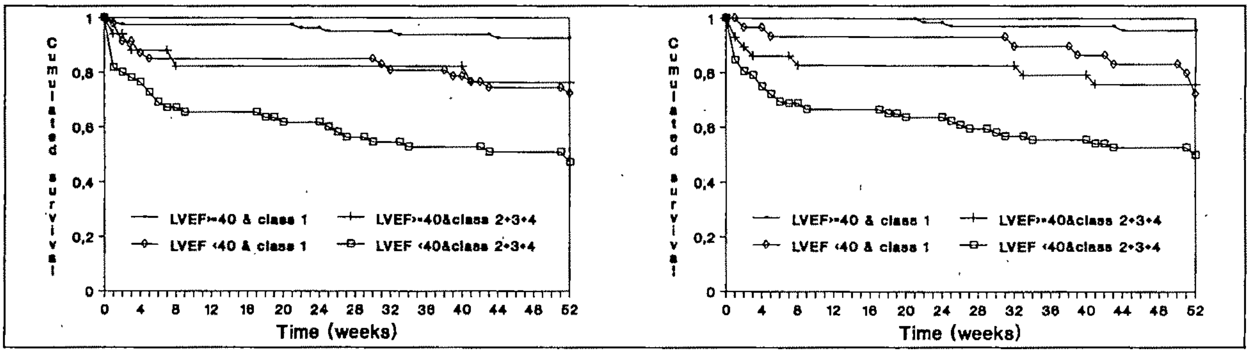


FIGURE 1. Kaplan-Meier survival curves showing 1-year mortality after acute myocardial infarction for combination of early *(left)* and maximal *(right)* Killip classes, and early left ventricular ejection fraction (LVEF). *Each plot* shows 4 prognostic groups. Numbers of deaths/patients in the 4 groups were *(left)* 6/86, 13/47, 4/17 and 29/82, and *(right)* 3/70, 6/30, 7/29 and 36/72, respectively. There were no significant differences between mortality in groups 2 and 3 ($p > 0.05$). Patients with early clinical signs of heart failure and LVEF ≥ 40 (4/17) have similar prognosis to those without heart failure but with LVEF <40 (13/47). In all, 64 of 201 patients (32%) *(left)* and 59 of 201 (29%) *(right)* belonged to 1 of these 2 categories. Thus, although observation of clinical heart failure on admission did not contain independent prognostic information, as judged by Cox model, it contributed to prognostic differentiation of patients characterized by echocardiographic LVEF, as judged by Kaplan-Meier survival curves.[11–16]

$\exp - [0.051 \times \exp[0.044 \times (\text{age} - 60) - 0.117 \times (\text{LVEF} - 40)]]$. Similarly, based on Cox regression model, the following algorithm was developed for predischarge calculation of risk of mortality at 1 year, using maximal in-hospital Killip class (maxKillip) and an early echocardiographic estimate of LVEF: $1 - \exp - [0.101 \times \exp[0.408 \times (\text{maxKillip} - 1) - 0.061 \times (\text{LVEF} - 40)]]$.

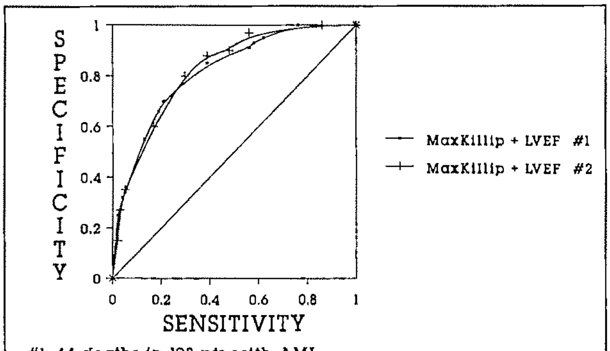
The validity of this prediction was tested in an independent, consecutive population of 195 patients with AMI with 40 deaths within 1 year in which resting echocardiograms were prospectively recorded at day 5. The original population of 201 patients was adjusted for deaths occurring before day 5 to match the new population, leaving a study population of 193 patients with 44 deaths within 1 year. The 2 receiver-operating characteristic curves were compared, and no statistical difference between the performance of the algorithm in the 2 populations was found (Figure 2).[19]

Because the algorithms are mathematically complex, a graphic display for practical use is provided in Figure 3.

DISCUSSION

Our observations in this unselected series of patients examined by echocardiography confirm the prognostic value of clinical and objective measures of myocardial damage in AMI (Table I). Furthermore, the data show that the prognostic strength of objective measures of global function relative to clinical heart failure is greatest in the first days during AMI and that clinical heart failure in terms of Killip class as a prognostic descriptor achieves prognostic strength by repeated observations, simply because it often takes time for myocardial failure to become clinically manifest (Tables II and III).

Another cause of the relative weakness of early clinical heart failure as a prognostic marker for prediction of



#1: 44 deaths in 193 pts with AMI
#2: 40 deaths in 195 pts with AMI

FIGURE 2. Receiver-operating curves comparing the value of predischarge prognostic algorithm (5 days after acute myocardial infarction [AMI]) for prediction of 1-year mortality in 2 independent populations. The algorithm was developed by retrospective analysis of mortality in a test of 201 patients without thrombolysis, and prospectively applied in a new independent control series of 195 patients. In the latter population, all patients received aspirin and 18% received thrombolytic therapy on admittance. There appears to be no statistical difference between the prediction of the algorithm in the 2 populations. LVEF = left ventricular ejection fraction; MaxKillip = maximal Killip class.

Table II Cox Models for Prediction of Death After Acute Myocardial Infarction Based on Early Echocardiographic Left Ventricular Ejection Fraction and Clinical Variables

Variables	2-Month Mortality Chi-Square	p Value
Prediction of Death After AMI by Early LVEF, Sex, Early Clinical Prognostic Index* and Maximal CKMB Value		
Early echocardiographic LVEF	18.78	<0.0001
Sex	1.11	NS
Early prognostic index*	1.00	NS
Maximal CKMB value	0.15	NS
Prediction of Death After AMI by Early LVEF and the 9 Clinical Variables Included in the Early Prognostic Index*		
Early echocardiographic LVEF	27.45	<0.0001
Age	6.51	<0.01
AMI number	0.10	NS
Reinfarction	0.06	NS
Congestive failure	2.55	NS
Asystole	3.11	NS
VF	0.42	NS
VX/VT	1.10	NS
SVT	—	
Nodal rhythm	—	
Prediction of Death After AMI by Most Predictive Variables		
Early echocardiographic LVEF	43.97	<0.0001
Age	6.35	<0.03

*Prognostic index was calculated 5 days after AMI on the basis of 9 clinical variables.[12]
Cox regression model for hazards and log-likelihood method; Analysis of all AMI patients (n = 201).
SVT = supraventricular tachycardia; VF = ventricular fibrillation; VT = ventricular tachycardia; VX = ventricular premature complexes; other abbreviations as in Table I.

Table III Cox Models for Prediction of Death After Acute Myocardial Infarction Based on Early Echocardiographic Left Ventricular Ejection Fraction and Late Clinical Variables

Variables	1-Year Mortality Chi-Square	p Value
Prediction of Death After AMI by Early LVEF, Sex, Late Clinical Prognostic Index* and Maximal CKMB Value		
Early echocardiographic LVEF	14.27	<0.0001
Sex	1.56	NS
Late prognostic index*	2.72	NS
Maximal CKMB value	0.64	NS
Prediction of Death After AMI by Early LVEF and the 9 Clinical Variables Included in the Late Prognostic Index*		
Early echocardiographic LVEF	10.87	<0.001
Age	0.54	NS
AMI number	1.95	NS
Reinfarction	0.46	NS
Congestive failure	1.07	NS
Asystole	0.81	NS
VF	1.06	NS
VX/VT	1.08	NS
SVT	—	NS
Nodal rhythm	—	
Prediction of Death After AMI by Most Predictive Variables		
Early echocardiographic LVEF	12.13	<0.001
Maximal Killip class	4.81	<0.05

*Late prognostic index was calculated predischarge on basis of 9 clinical variables.[12]
Cox regression model for hazards and log-likelihood method; analysis of all AMI patients discharged alive.
Abbreviations as in Tables I and II.

mortality compared with objective measures of left ventricular systolic performance is explained by the confounding, multifactorial nature of the manifestations of clinical heart failure, which are reflectors of the interplay between systolic and diastolic myocardial function, as modulated by acute changes in preload, afterload and pericardial stiffness. Recently, the discrepancies between clinical evaluation of heart failure and objective measures of systolic myocardial performance in acute AMI were stressed.[3,20,21]

Early prediction of 2-month mortality after AMI was maximized by integrating age and echocardiographic LVEF, which are parameters that in principle can be instantly available on admittance (Table II). This appears useful for simple, early routine baseline risk stratification, allowing immediate identification of the large subset of low-risk patients after AMI who are candidates for early discharge and exclusion from controlled clinical mortality studies, because their risk of dying within 2 to 12 months is small.[3] At the same time, it allows immediate identification of patients most likely to develop heart failure or shock who are potential targets of early intensive management.[22] Predischarge prognosis in the present series was best evaluated by combining information on LVEF and maximal Killip class at discharge, which currently has obtained independent prognostic value, whereas the independent prognostic value of age was lost (Table III). This shift of relative prognostic value of age and heart failure was probably also due to the fact that a number of patients at particularly high age and risk died before discharge, and accordingly were not included in the development of the algorithm for calculation of predischarge risk.

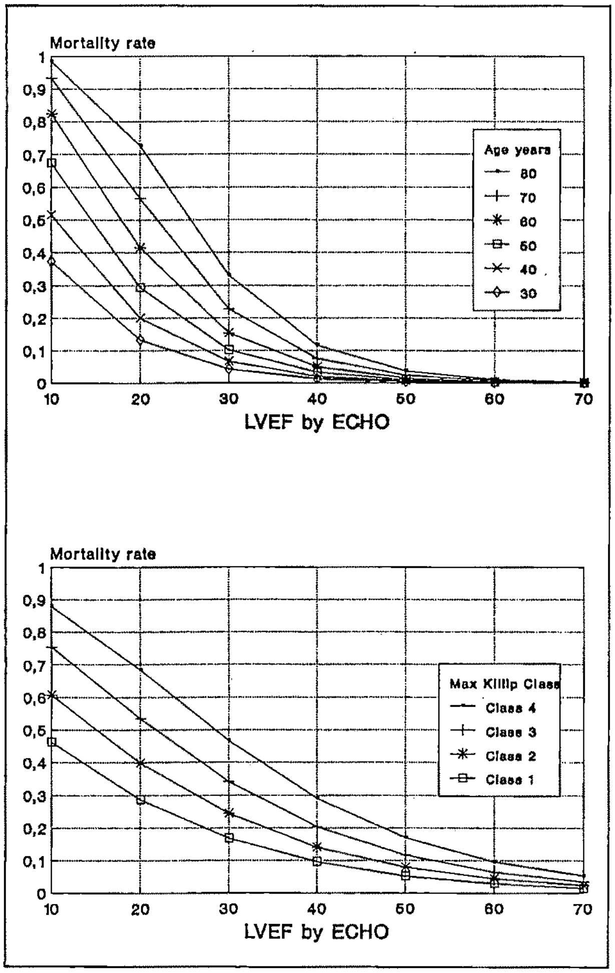


FIGURE 3. Graphic display providing impression of performance of optimized prognostic admission and predischarge algorithms. *Top,* relation between 2-month mortality, age and left ventricular ejection fraction (LVEF) on admission. *Bottom,* relation between 1-year mortality, maximal (Max) Killip class at discharge, and early LVEF. Graphs can be used to read risk of mortality after acute myocardial infarction, obviating the need for calculations. On early risk assessment, patient aged 40 years with LVEF of 60 would have 0.2% risk of dying within 2 months, whereas patient aged 70 years with LVEF of 20 would have 57% risk of dying *(top).* On predischarge assessment of risk, patient without in-hospital heart failure and early LVEF of 60 would have 3% risk of dying within 1 year, whereas patient without in-hospital heart failure and LVEF <30 would have similar risk of 17% *(bottom).* ECHO = echocardiography.

Although the described algorithms were mathematically complex, the calculation of risk of mortality was relatively simple based on an early echocardiographic wall motion-derived estimation of LVEF, the age of the patient, and observations on heart failure, which are or can be routinely available in a large number of coronary care units. Tibbits et al[23] showed that although broadly used predischarge testing of risk of mortality or repeat AMI within 1 year after AMI provided a statistically significant improvement of assessment of risk, this appeared to be of little clinical relevance. McNamara et al[15] reported that LVEF at discharge could be predicted based on simple clinical observations in 72% of patients after AMI, with <10% frequency of large errors. In contrast, the algorithms proposed in this study were based on broadly applied early testing by echocardiography on admission comprising both in-hospital and predischarge evaluations of risk in 1 examination. This type of risk stratification may be particularly relevant for research protocols to characterize groups of patients, but may even be justified for optimal, clinical routine management decisions in individual patients (early discharge/aggressive treatment) (Figure 3).[3]

Our study confirms that early echocardiographic wall motion analysis has useful prognostic information in AMI and that translation of wall motion data into clinically meaningful LVEF values is feasible (Tables II and III, and Figures 1 and 3).[2–5,7] This translation circumvents some of the standardization problems caused by the many formats of wall motion indexes used in the past. The evaluation of left ventricular global function is facilitated by using high segmental score values for normal function, and low values for poor function in analogy with LVEF values, and needs the assignment of a specific score value for hyperkinesia. Obviously, when converting echocardiographic wall motion index values into LVEF values, we are dealing with estimates, not measurements, of LVEF, and other imaging methods are known to provide more accurate measurements of LVEF. Furthermore, observations of wall motion neither provide measures of volumes nor degree of distortion of left ventricular shape, which are necessary to characterize the remodeling process.[24] However, this may be unimportant in the context of prognostication in AMI, if such measures do not convey more accurate prognostic information than does wall motion, which is much easier to obtain. Jugdutt[25] stressed the significance of ventricular shape, and White et al[26] stressed the importance of end-systolic volumes, but further studies are clearly needed to define the relative prognostic role of early wall motion, volumes and indexes of cavity shape after AMI, as well as diastolic parameters of possible additional prognostic merit.[27]

Although the observation of early heart failure did not obtain independent prognostic information in the present series when LVEF was included in the Cox model, it added significant complementary prognostic information to LVEF (Figure 1). This was also reported by other investigators who used radionuclide angiography for measuring LVEF at various points of time during AMI in selected groups of patients.[9-11]

Study limitations: All 201 patients in the test series were examined in the prethrombolytic era, which is important because recovery of left ventricular global function after AMI is more pronounced after thrombolysis with reperfusion.[28,29] However, the improvement of left ventricular function after thrombolysis is often relatively small.[29,30] Furthermore, a large subset of patients with AMI, depending on time factors and local practice, still does not receive thrombolytic treatment. Our prognostic algorithms should be useful in this group of patients without reservation. No information on coronary artery patency was available in the patients, precluding analysis of the prognostic relations between reperfusion, coronary artery patency and ventricular performance.[30] However, the data show that the prognostic algorithm developed in the test series of 201 patients who did not receive thrombolysis was also valid in the control series of 195 who were routinely treated with aspirin on admission, and 18% of whom received thrombolytic treatment. This suggests that our algorithms may be generally useful in large, unselected populations of patients with AMI whether treated with thrombolytic agents or not, although admittedly, the algorithms are inaccurate in patients who experience a dramatic spontaneous or post-thrombolytic recovery of early left ventricular function. Larger, consecutive series of unselected patients receiving thrombolytic therapy should be studied to firmly define the value of an early echocardiogram for prediction of mortality after AMI in the growing group of patients that receive reperfusion therapy.

The proposed, simple method of establishing baseline prognostics during AMI by estimating early resting LVEF, and recording signs of heart failure and age, only refers to mortality and does not attempt to predict the risk of nonfatal ischemic complications or electrophysiologic events of possible additional merit for prediction of (sudden) death. However, such predictions rely on broadly used testing that is not available during early AMI (exercise and other stress testing) and that may not be feasible or justified in unselected populations in the predischarge setting.[23]

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Electrocardiographic Criteria for Diagnosis of Acute Myocardial Infarction in Childhood

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Myocardial infarction (MI), a common occurrence in adults, is generally considered to be rare in children. Electrocardiographic criteria for diagnosis of MI in adults are well known and accepted, but no general criteria exist for children. We report 37 autopsy-proved cases of transmural MI and electrocardiographic evidence of MI in 30 of these cases. A variety of conditions previously reported to produce "pseudo-infarction" are included in these cases of MI, including myocarditis, hypertrophic cardiomyopathy, and the cardiomyopathy of Duchenne's muscular dystrophy. Compilation of the electrocardiographic data in all patients allowed for the development of criteria for this diagnosis of MI in childhood, and include wide Q waves (>35 ms) with or without Q-wave notching, ST-segment elevation (>2 mm), and prolonged QT interval corrected for heart rate (QTc >440 ms) with accompanying Q-wave abnormalities. With use of these electrocardiographic criteria, an additional 3 patients were subsequently diagnosed prospectively with MI and confirmed on autopsy. Pathologic evaluation confirmed the location of infarction predicted by the electrocardiograms in all 3 cases.

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Myocardial infarction (MI) is among the most prevalent conditions in the United States, accounting for significant mortality and morbidity in adults. Diagnostic criteria for MI in adults have been established for electrocardiography, echocardiography, serum enzymes and radiopharmaceutical scans,[1,2] but these criteria have either not been evaluated extensively in children or are not considered useful. No diagnostic electrocardiographic criteria have been established for MI in children. Fujiwara et al[3] described the electrocardiographic findings of MI in Kawasaki disease with giant coronary artery aneurysms. Deep Q waves or new-onset Q waves in the limb leads were considered indicators of MI and have subsequently been confirmed.[4–6] However, these findings appear to differ from that seen in childhood MI because of etiologies other than Kawasaki disease. The width of the Q wave, and not its depth, has been considered to be the important diagnostic parameter in these disorders.[4,7–10] QRS or Q-wave notching has been described in adults[11–15] but is rarely noted in children.[16] Notching has been shown to be both predictive of MI and the eventual outcome in adults,[11] but no definitive conclusions regarding the value of Q-wave notching in the diagnoses of childhood MI have been formulated. The purpose of this study was to develop diagnostic electrocardiographic criteria for MI in childhood, including those secondary to congenital or acquired diseases.

METHODS

All autopsy specimens from Texas Children's Hospital (1952 to 1987) demonstrating transmural MI in patients aged <21 years (range 2 days to 20 years) were reviewed retrospectively. Patient records and available electrocardiograms were evaluated. Electrocardiograms obtained from patients with comparable diagnoses but without pathologic evidence of MI were also reviewed. Prospective pathologic examination was performed on those specimens obtained at autopsy from children with electrocardiographic evidence of MI before death.

Electrocardiography: All electrocardiograms were performed at Texas Children's Hospital using a Cambridge or Marquette electrocardiograph. The paper speed was 25 mm/s, filters were set at 0 to 100 Hz, and amplitude was standard throughout the study period. Serial 15-lead (standard 12 leads plus V_3R, V_4R, V_7) tracings were performed and compared with age-matched normal values.[7,17,18]

Q-wave notching was defined as any abrupt change in the smooth contour of the Q wave, including slurring or changes in direction (negative to positive or vice versa) of the Q-wave deflection. QTc was measured in lead II or the lead in which the QT interval was longest, and was defined as the QT interval corrected for heart

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TABLE I Q-Wave Duration

Lead	No Q-Wave	Q-Wave Duration <35 ms	>35 ms	Range (ms)	Mean (ms)
I	10	7	20	33–48	43
III	12	8	17	30–43	37
V_1	16	6	15	34–51	46
V_3	20	5	12	32–46	43
V_6	10	10	17	29–40	35

Twenty-five of 37 patients had at least 1 abnormal lead. Twenty-one of 37 had location predicted successfully.

rate as described by Bazett's formula.[19] QTc <440 ms is normal for children.[7,17]

Abnormalities of Q-wave amplitude in children were based on modification of the data reported by Nakanishi et al.[4]

Pathology: Standard pathologic criteria for acute and nonacute MI were used.[1,20–22]

RESULTS

Thirty-seven autopsy specimens with the diagnosis of transmural MI in patients aged <21 years were studied retrospectively. All patients had ≥1 electrocardiogram recorded before death. The distribution of diseases in which MI occurred is shown in Figure 1.

Anomalous left coronary artery originating from the pulmonary artery was the most frequently associated congenital cardiovascular disease in which MI occurred (24%), whereas Kawasaki disease was the most frequently acquired cause and the second most frequently acquired cause overall (19%). Less frequent etiologies are shown in Figure 1 and include those listed as well as systemic lupus erythematosis, lymphoma and postoperative heart transplantation (noted in the figure as "other"). All infarctions were found in the hypertrophied ventricle (i.e., left ventricle in aortic stenosis, right ventricle in pulmonary atresia–intact ventricular septum) when cardiac hypertrophy was in evidence.

Pathologic evaluation of the specimens retrospectively studied demonstrated an acute MI in 28 of the 37 cases (75%). All infarctions categorized pathologically as acute transmural infarctions had electrocardiographic features satisfying adult criteria for MI. Only 2 of 9 (22%) nonacute infarctions by pathologic criteria had electrocardiographic evidence of MI (wide Q waves, QTc >440 ms), both with hypertrophic cardiomyopathy. Therefore, by electrocardiography, 30 of the 37 autopsy-proved cases of transmural MI were retrospectively diagnosed on electrocardiography. The 7 remaining retrospective tracings with nonacute MI were normal. No patient had prior electrocardiograms consistent with MI. These included 2 toddlers with anomalous left coronary artery not diagnosed in infancy, 2 patients with perinatal asphyxia, 1 patient with chronic myocarditis, 1 patient with systemic lupus erythematosis, and 1 child with pulmonary atresia–intact ventricular septum. The 30 abnormal electrocardiograms (28 with acute MI, 2 with nonacute MI) studied retrospectively were used to establish the criteria for MI in childhood. The salient features of the electrocardiographic measurements in these 30 cases compared with age-matched normal values are as follows:

1. *Q-wave amplitude:* Q waves in lead III ranged from 1 to 20 mm (mean 4.8 mm), with 8 of 37 (22%) falling outside the normal range. Abnormally deep Q waves in 7 of 8 patients were found in lead III in patients with Kawasaki disease and giant coronary aneurysms. Q-wave amplitude in lead V_6 ranged from 0 to 11 mm (mean 3.6 mm); only 3 of 37 (8%) appeared abnormally deep. In addition, 6 of the children with Kawasaki disease also had deep Q waves in lead V_1.

2. *Q-wave duration* (*Table I*): Salient features include prolonged Q-wave duration in leads I, III, V_1, V_3 and V_6 (≥35 ms). Lead I was most frequently prolonged (20 of 37 cases, 54%) followed by leads III and V_6 (17 of 37 cases, 46%). In 24 of the 37 autopsy-

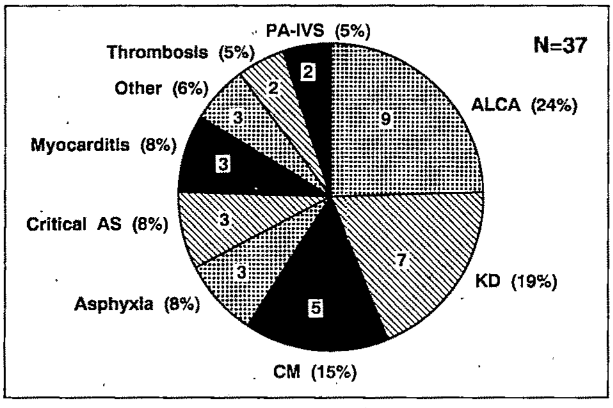

FIGURE 1. Myocardial infarction in childhood. The distribution of cardiac disorders in 37 patients in which myocardial infarction occurred as seen at autopsy. ALCA = anomalous left coronary artery from the pulmonary artery; AS = aortic stenosis; CM = cardiomyopathy; KD = Kawasaki disease; PA-IVS = pulmonary atresia with intact ventricular septum.

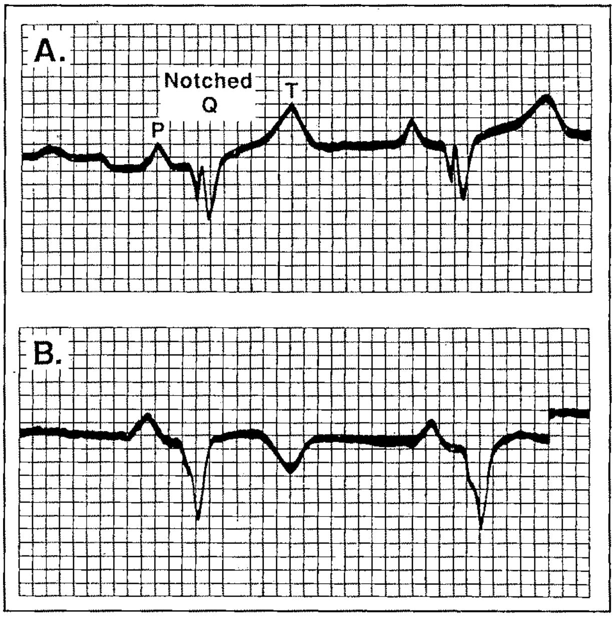

FIGURE 2. Notched Q waves, with 2 different patterns of Q-wave notching in childhood myocardial infarction. *A.*, deeply notched Q wave in QSQ'S' pattern. Normal P wave and upright T wave also shown. *B.*, subtle Q-wave notching. Normal P wave and inverted T wave shown.

TABLE II ST-Segment Elevation

Lead	Range (mm)	Mean (mm)	Abnormal (no.)	(>2 mm) %
I	0–6	4	12	32
III	0–4	3	10	27
V$_1$	0–5	3	9	24
V$_3$	0–6	4	14	38
V$_6$	0–4	2	10	27

proved specimens (65%), at least 1 lead had abnormal Q-wave prolongation and in 21 of these cases, the location of the infarction seen pathologically was successfully predicted on the basis of the Q-wave location. A single patient with Kawasaki disease had both deep and wide Q waves.

3. *Q-wave contour:* The 2 forms of notched Q waves seen (Figure 2) were wide, stair-stepped Q waves, and more subtle notched and slurred Q waves. Notching was found most frequently in leads I (3 of 37 cases, 8%) and III (3 of 37). Each of the precordial leads (V$_1$, V$_3$ and V$_6$) had notching in 2 of 37 cases (5%), respectively. In all, 6 of 37 patients had at least 1 lead with Q-wave notching.

4. *QT intervals:* QTc ranged from 350 to 480 ms (mean QTc 440 ms), with 20 of 37 tracings demonstrating abnormally prolonged intervals (>440 ms).

5. *ST segment* (*Table II*): Twenty-five tracings had leads with ST segment elevations >2 mm; 22 of these children had acute MI, whereas only 3 had nonacute MI. The lead most frequently abnormal was lead I (mean 4 mm). The elevation exceeded 2 mm (and was therefore abnormal) in 12 of 37 patients (32%). Only lead III had ST segment abnormalities (14 of 37, 37%).

These electrocardiographic criteria were used to prospectively diagnose acute transmural MI in 6 patients (1 with critical aortic stenosis, 1 with anomalous left coronary artery, 1 with postoperative transplant, 2 with myocarditis, 1 with pulmonary atresia–intact ventricular septum) who were later confirmed by autopsy to have MI. In addition, 30 tracings were reviewed from patients with each comparable diagnosis but without pathologic evidence of MI, except for anomalous left coronary artery in which only 10 cases without MI could be found. No abnormal Q waves occurred in comparable patients with anomalous left coronary artery or Kawasaki disease having no pathologic evidence of MI. In patients with hypertrophied ventricles but no pathologic evidence of MI (aortic stenosis, hypertrophic cardiomyopathy, or pulmonary atresia with intact ventricular septum), only deep Q waves were seen. No patient with comparable diagnosis but without pathologic evidence of MI had wide Q waves.

DISCUSSION

MI may occur in children with a wide variety of congenital and acquired cardiac diseases (Table III). These include congenital cardiac disorders with coronary artery abnormalities as well as those causing ventricular hypertrophy. In the latter, the areas of necrosis are thought to occur in those with the most severe hypertrophy.[10,20-22] The electrocardiographic and patho-

TABLE III Reported Causes of Myocardial Infarction in Children: Classified by Pathophysiologic Mechanisms

- Coronary artery occlusion
- Arteritis
  - Kawasaki disease*
  - Coronary artery vasculitis
  - Rheumatic carditis
  - Systemic lupus erythematosus*
  - Takayasu's disease
  - Periarteritis nodosa
  - Transplant rejection*
- Coronary vasospasm
  - Cocaine abuse
  - Glue sniffing
  - Migraine headache
- Thrombi/emboli to coronary artery
  - Coronary artery thrombosis
  - Intrauterine coronary artery embolism
  - Mitral valve prolapse
  - Lymphoma*
  - Ventricular tumor
  - Sickle cell disease
  - Umbilical cord hematoma
  - Thromboembolism from umbilical vein
  - Thromboembolism from ductus venosus
  - Thromboembolism from intrauterine renal vein thrombosis
  - Infective endocarditis
  - Hemophilia treated with unactivated prothrombin complex concentrates
- Coronary mural thickening with metabolic diseases or intimal proliferation disease
  - Progeria
  - Pseudoxanthoma elasticum
  - Mucopolysaccharidosis
  - Fabry's disease
  - Alkaptonuria
  - Hurler syndrome
  - Birth control pills/pregnancy
  - Premature atherosclerotic heart disease
  - Transplant coronary heart disease*
  - Hyperbetalipoproteinemia
- Other
  - Idiopathic calcification of the coronary arteries
  - Blunt chest trauma
  - Coronary artery stenosis/single coronary artery
  - Surgical trauma
  - Postoperative arterial switch (Jatene) procedure
  - Disseminated intravascular coagulation
- Coronary hypoperfusion
- Congenital coronary artery anomalies
  - Anomalous origin of the left coronary artery*
  - Transposition of the great vessels
- Myocardial oxygen supply-demand mismatch
  - Perinatal asphyxia*
  - Cardiomyopathy*
  - Critical congenital aortic stenosis*
  - Myocarditis*
  - Pulmonary atresia with intact ventricular septum*
  - Supravalvar aortic stenosis: Williams syndrome
  - Coarctation of the aorta with/without Turner's syndrome
  - Hypoplastic left heart syndrome
  - Aortic thrombosis
  - Erythroblastosis
- Congenital cardiac disease
  - Total anomalous pulmonary venous connection
  - Congenital pulmonary stenosis (severe)
  - Truncus arteriosus

*Disorders associated with myocardial infarction in this report logic correlates in our patients support this hypothesis; when hypertrophy was in evidence, the infarcted region was found in that hypertrophied ventricle.

The electrocardiographic data compiled in this study demonstrate that the finding most specific for childhood MI is wide Q waves (transmural MI), >35 ms in duration, especially when this is a new finding, and suggest that the diagnosis of acute transmural MI should not be made in the absence of Q-wave abnormalities on electrocardiography. Q-wave notching occurred in a high percentage of children with MI (16%) and in all instances correctly predicted its location. In adults it has been suggested that a poorer outcome occurs in patients with notched Q waves than in patients without electrocardiographic evidence of notching.[11,12] The high incidence of Q-wave notching in our autopsy-proved cases of childhood MI may also indicate that this is a poor prognostic sign; however, this cannot be ascertained directly from this study because only autopsy specimens were used. Unlike adults with MI, deep Q waves were diagnostic of MI only in children with Kawasaki disease and giant coronary aneurysms. The data support the view that deep Q waves should be a criteria for MI only in the presence of known or suspected history of Kawasaki disease. The distribution of abnormal Q waves in Kawasaki disease was similar to that described by Fujiwara[3] and Nakanishi[4] and their co-workers. Nakanishi et al[4] showed that both Q-wave amplitude and duration is specific (97 to 100%) for diagnosing inferior MI, but that only amplitude is sensitive for the diagnosis (86%) in patients with Kawasaki disease. In anterior and lateral infarctions, however, high sensitivity (85%) was seen only when both amplitude and duration of Q waves were abnormal. On serial tracings, new-onset Q waves or increased depth of preexisting Q waves correlated with new areas of necrosis.

These accumulated electrocardiographic measurements therefore allow for establishment of electrocardiographic criteria in the diagnosis of acute childhood MI and include the following: (1) new appearance of wide Q waves >35 ms in duration, (2) increased amplitude or duration (>35 ms) of preexisting Q waves, (3) new-onset Q waves in serial tracings, (4) Q-wave notching, and (5) ST segment elevation ≥2 mm and prolonged QTc >440 ms when associated with any other criterion.

In 30 of 37 retrospective cases, 1 or more of these criteria was associated with the autopsy-proved diagnosis of MI. Three patients prospectively evaluated with electrocardiograms meeting these diagnostic criteria subsequently had infarctions confirmed by autopsy.

We conclude that electrocardiography is useful in the diagnosis of acute transmural MI in children and that the electrocardiographic criteria outlined in this report are sensitive for this diagnosis. These criteria appear less useful for the diagnoses of nonacute MI in the pediatric population.

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Frequency of Coronary Artery Disease and Left Ventricular Dysfunction in Cocaine Users

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To evaluate the spectrum of coronary artery disease (CAD) in cocaine users, coronary angiograms obtained from 33 patients (26 men [79%] and 7 women [21%], mean age 37 years) with history of cocaine use and cardiac symptoms were retrospectively reviewed. Clinical indications for coronary angiograms included chest pain (n = 28), congestive failure (n = 4) and complete heart block (n = 1). Coronary angiograms were reviewed independently by 2 angiographers unaware of patient's clinical status. Thirteen patients (40%) had normal coronary angiograms, and 20 (60%) had CAD; 7 (21%) had mild CAD ($\leq$70% diameter stenosis), and 13 (40%) had significant CAD ($>$70% diameter stenosis). Of 13 patients with significant CAD, 7 had 1-vessel, 4 had 2-vessel and 2 had 3-vessel CAD. There was enzymatic evidence of myocardial infarction in 12 of 33 patients (36%); all 12 had CAD (10 with significant and 2 with mild CAD). Mean age and number of risk factors (serum total cholesterol, cigarette smoking, systemic hypertension, diabetes mellitus, family history of CAD, and obesity) in patients with CAD (mild or significant) and with normal coronary angiograms were not statistically different. Left ventricular ejection fraction was normal in 15 patients (45%) and depressed in 18 (55%). All patients with CAD and low ejection fractions (n = 12) had regional wall motion abnormalities, whereas all those with normal coronary arteries and low ejection fractions (n = 6) had global hypokinesia.

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Recently, the number of emergency room evaluations of cocaine users has markedly increased because of an increase in the use of cocaine and crack cocaine (which is more potent than cocaine).[1] Chest pain is a frequent presenting symptom in these patients. Causes of chest pain in cocaine users include myocardial ischemia and infarction,[2–5] myocarditis,[6,7] aortic dissection[8,9] and pneumomediastinum.[10] In cocaine users, myocardial infarction could occur secondary to coronary artery spasm,[11,12] formation of thrombus in normal or mildly stenotic coronary arteries,[2,6,13,14] or simply an imbalance of the supply and demand of oxygen due to excessive tachycardia and hypertension. Although several autopsy studies have demonstrated coronary stenotic lesions in cocaine users,[6,7,14–16] only a few studies have evaluated coronary artery disease (CAD) in cocaine users.[3,17,18] The presence of significant CAD in young cocaine users with relatively low cardiovascular risk factors raises the question of whether cocaine enhances atherosclerosis. In the present study, we describe the angiographic spectrum of CAD and left ventricular dysfunction in patients with history of cocaine use.

METHODS

Patients: We reviewed the medical records of 33 patients with history of cocaine use admitted to the Medical College of Virginia in whom the clinical presentation prompted referral for coronary angiography by the attending physician. Urine toxicology screen in all 33 patients was positive for cocaine, although 16 denied recent cocaine use. All patients were admitted to the coronary intensive care unit to rule out myocardial infarction, and had serial electrocardiographic and cardiac enzyme monitoring. Medical records were reviewed for demographic details, risk factors (cigarette smoking, systemic hypertension, family history of CAD aged <55 years, diabetes mellitus, obesity and serum total cholesterol), history of alcohol consumption, and laboratory values. Hypertension was defined as a positive history and diastolic blood pressure >95 mm Hg on multiple occasions after admission, and obesity was defined as $\geq$20% above expected weight. No patient had history of angina or other cardiac events. In 13 patients, medical records were complete, whereas additional details of risk factors were obtained by telephone in 20 patients after hospital discharge.

Coronary angiography: Cardiac catheterization with coronary angiography and left ventriculography was performed by the Judkins technique, and multiple views were obtained to evaluate the coronary arteries. Coronary angiograms were reviewed independently by 2 experienced angiographers with joint agreement who were unaware of the patient's clinical status. All steno-

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TABLE I Risk Factors in Patients with Normal Coronary Arteries (group 1) and Coronary Artery Disease (group 2)

	Group 1 (n = 13)	Group 2 (n = 20)
Mean age (yr)	37	37
Men/women	10/3	16/4
Systemic hypertension	2	3
Cigarette smoking	8	16
Mean serum total cholesterol (mg/dl)	158	162
Diabetes mellitus	0	1
Obesity ($\geq$20% above expected weight)	1	1
Family history of coronary artery disease at <55 years	5	4

TABLE II Summary of Published Studies Evaluating Coronary Artery Disease in Cocaine Users

Study	No. of Pts.	Mean Age (yrs)	Method of Study	Pts. with >75% Coronary Stenosis
Amin et al[18]	8	—	Angiography	4
Kossowsky & Lyon[5]	4	36	Angiography	4
Pasternak et al[3]	3	34	Angiography	3
Virmani et al[6]	40	—	Autopsy	2
Mittleman & Wetli[22]	24	47	Autopsy	15
Tazelaar et al[24]	30	34	Autopsy	0
Dressler et al[15]	22	32	Autopsy	8
Simpson & Edward[14]	1	21	Autopsy	1
Isner[7]	1	37	Autopsy	1
Stenberg et al[23]	1	38	Autopsy	1

ses were evaluated by calipers for diameter assessment. Significant CAD was defined as $>70\%$ reduction in luminal diameter of ≥ 1 coronary artery, and reduction in the luminal diameter of $\leq 70\%$ was characterized as nonsignificant CAD. Left ventricular ejection fraction for each patient was calculated by planimetry.

RESULTS

Demographic details: Twenty-seven patients were men and 6 were women (mean age 37 years, range 24 to 59). The presenting symptom was chest pain in 28 patients and congestive heart failure in 4, and 1 had dizziness on admission and was found to be in third-degree heart block. Fifteen patients predominantly used cocaine intravenously, 9 by smoking, and 6 by sniffing, whereas the route of administration was not known in 3. There was no difference in the route of cocaine administration in patients with and without CAD. The frequency and quantity of cocaine use could not be reliably obtained, because most patients gave different histories on different occasions.

Risk factors: Total number of risk factors in patients with normal coronary arteries (group 1) and CAD (group 2) were similar (Table I). Mean age of patients in both groups was 37 years and the men/women ratios were similar. Although a higher percentage of patients in group 2 (80%) had history of cigarette smoking than did those in group 1 (62%), the difference was not statistically significant. Four patients had no cardiovascular risk factor, 14 had 1 factor, 12 had 2 factors, and 3 had 3 factors. All 33 patients had history of alcohol consumption. The amount of alcohol consumed could not be reliably obtained.

Coronary angiography: Of the 33 patients, 13 (40%) had normal coronary arteries, whereas 20 (60%) had CAD (13 [40%] significant and 7 [20%] nonsignificant). Of 13 patients with significant CAD, 7 had 1-vessel, 4 had 2-vessel and 2 had 3-vessel CAD.

Myocardial infarction: There was enzymatic evidence of myocardial infarction in 12 of 33 patients (36%) after admission. Six patients (50%) had Q-wave and 6 (50%) had non-Q-wave myocardial infarction. Of these 12 patients, 10 had significant CAD (6 had Q-wave and 4 had non-Q-wave myocardial infarction). None of the 13 patients with normal coronary arteries had any evidence of myocardial infarction. Nine patients with significant CAD underwent percutaneous transluminal coronary angioplasty, and 1 had coronary artery bypass surgery.

Cardiomyopathy: Of the 33 patients, 15 (45%) had a normal ejection fraction, 12 (36%) had ejection fractions between 30 and 50%, and 6 (18%) had $\leq 30\%$. All 12 patients with either significant or nonsignificant CAD and ejection fraction $\leq 50\%$ had regional wall motion abnormalities reflecting recent or remote myocardial infarction. However, all 6 patients with normal coronary arteries and ejection fraction $\leq 50\%$ had global hypokinesia.

DISCUSSION

Cocaine blocks the presynaptic reuptake of norepinephrine and dopamine.[19] This sympathomimetic state causes generalized vasoconstriction that affects multiple organ systems. Resultant cardiovascular complications can be life-threatening. Myocardial infarction[2-5] is the most frequently reported cardiac complication of cocaine use. The pathophysiology of cocaine-induced myocardial infarction could be multifactorial. Spasm of normal and stenotic coronary arteries has been documented in the cardiac catheterization laboratory with 2 mg/kg of intranasal cocaine.[11] However, cocaine-induced coronary thrombosis has also been documented angiographically[2] and in autopsy studies.[6,14,16] It is not known whether cocaine enhances atherosclerosis. Preliminary work by Langner et al[20] demonstrated increased protein synthesis in the wall of the aorta compared with that in the liver of rabbits treated with cocaine. Prior studies showed that animals fed a high cholesterol diet will manifest increased protein synthesis not only in the aortic wall, but also in the liver. The selective increase of protein synthesis in the aortic wall of rabbits treated with cocaine may represent early atherosclerotic process.

Clinical evidence of cocaine-induced enhancement of atherosclerosis is lacking. In the present study, angiographic documentation of CAD in 20 of 33 cocaine users (60%) with relatively low cardiovascular risk factors was much higher than expected. For example, Roberts[21] demonstrated the presence of significant CAD (>75% luminal narrowing) in only 3% of histologic sections of coronary arteries of 40 patients (mean age 52 years) who died of leukemia with no expected cardiovascular disease.

This is the first angiographic study of a large number of cocaine users documenting the presence of CAD in 60% of patients studied because of cardiac symptoms. Similar results were documented in the autopsy study of coronary arteries in 22 cocaine users (mean age 32 years) by Dressler et al,[15] which revealed the presence of significant CAD (>75% reduction in cross-sectional area) in 8 patients (36%). Furthermore, a higher percentage of patients (15 of 24 [63%]) were found to have significant CAD by Mittleman and Wetli[22] in an autopsy study of 24 cocaine users (mean age 32 years). Presence of significant CAD in cocaine users was also documented angiographically in multiple small reports and other autopsy studies[23,24] (Table II).

The mechanisms by which cocaine could enhance atherosclerosis are not known. A recent study of cocaine users by Kolodgie et al[16] demonstrated the presence of a large number of mast cells in the areas of significant coronary artery stenosis. There was a significant correlation between the number of mast cells and the severity of CAD. Mast cells contain histamine and therefore could have an important role in the coronary vasospasm,[25] and by virtue of their role in lipid uptake[26] could be involved in the process of atherosclerosis. However, the role of mast cells in cocaine-associated atherosclerosis needs further evaluation.

Risk factors and coronary artery disease: It is estimated that 30 million people in the United States have used cocaine, and approximately 1 million use it on a regular basis. It is not known what predisposes a small number of cocaine users to its major complications. The predominant risk factor in our patients was cigarette smoking, which was not significantly different between patients with CAD (16 of 20 [80%]) and normal coronary arteries (8 of 13 [62%]). The route of cocaine administration was also not found to be different in the 2 groups. Cocaine is metabolized by liver and serum pseudocholinesterase enzyme.[27] Congenital deficiency of pseudocholinesterase is known,[28] with an estimated frequency of 1 in 50,000 to 100,000. Whether deficiency or low level of serum pseudocholinesterase predisposes cocaine users to its complications is currently under investigation.

Cocaine and left ventricular dysfunction: In animals, intravenous cocaine in high doses has been shown to cause acute ventricular dilatation and impairment of systolic function.[29] To establish a diagnosis of cocaine-induced cardiomyopathy, certain criteria should be met. Other causes of cardiomyopathy should be ruled out, and cardiac catheterization revealing normal coronary arteries should be documented. Clinical evidence of cocaine as the cause of dilated cardiomyopathy is limited. In our study, 12 of 20 patients (60%) with angiographically documented CAD (significant or nonsignificant) had an ejection fraction ≤50% with regional wall motion abnormalities reflecting recent or remote myocardial infarction. However, 6 patients with normal coronary arteries had ejection fraction ≤50% (4 with ejection fraction <30%) and global hypokinesia. All 33 patients had history of alcohol consumption. Details of the quantity of alcohol consumed could not be reliably obtained. Therefore, it was not possible to establish cocaine as a direct cause of dilated cardiomyopathy. However, this distinction may be difficult clinically, because alcohol is almost always associated with cocaine use. If cocaine produces cardiomyopathy, the mechanism of its causation is not known. The possible mechanisms include a direct myocardial depression[29] or excess catecholamines.[30]

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Preoperative Coronary Artery Disease Risk Stratification Based on Dipyridamole Imaging and a Simple Three-Step, Three-Segment Model for Patients Undergoing Noncardiac Vascular Surgery or Major General Surgery

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A 3-step, 3-segment scintigraphic model was developed to improve the accuracy of dipyridamole-thallium imaging for preoperative cardiac risk assessment and to simplify the prognostic interpretation of the images. The model was developed in a pilot study of 60 patients and validated in a group of 355 patients referred for vascular and major general surgery. Study end points included myocardial infarction and cardiac death. Step 1: The postoperative cardiac event rate was 1.3% in 225 patients with normal anterior, inferio- and posterolateral segment perfusion and without transient left ventricular dipyridamole-induced cavitary dilation. Step 2: The physiologic rationale for step 2 consists of identifying patients who are most likely to have left main, 3-vessel or high-risk 2-vessel coronary artery disease or a significant amount of jeopardized myocardium in the territory of a critical coronary stenosis. Of 29 patients with either reversible defects of all 3 segments, transient cavitary dilation, or at least 1 severe grade 3/3 reversible defect, 52% (15 of 29) sustained a postoperative cardiac event. Step 3: The remaining 101 patients were stratified according to age >70 years ($p = 0.01$), presence of diabetes ($p = 0.0004$) and the number of segments displaying reversible defects (1 or 2) with cardiac event rates ranging from 5 to 36%. The 3-step, 3-segment model is a useful alternative to the conventional interpretation of dipyridamole myocardial perfusion images for the purpose of quick and efficient preoperative risk stratification based on the rationale of correlating surgical risk with the amount of potentially ischemic myocardium. With step 1 (low risk) 63% (225 of 355) of the patients have been classified, whereas with step 2 (high risk), 50% (15 of 30) of the complications could have been avoided.

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Dipyridamole-thallium imaging is routinely performed for risk stratification before noncardiac surgery in patients who cannot achieve an adequate heart rate on the treadmill. Most investigators recommend preoperative coronary angiography in patients with thallium redistribution.[1-10] Because the sensitivity of this finding for the presence of coronary artery disease is approximately 85%,[11] this strategy results in preoperative arteriography being performed and revascularization considered in most patients with coronary artery disease. In a previous study, we showed that quantitative indexes reflecting the severity and extent of reversible perfusion defects could be used to improve the specificity of the test and restrict the requirement of preoperative coronary angiography to a small subset of patients.[12] However, the quantitative technique described was time-consuming and required minutia, thus limiting its widespread application and reproducibility in a busy clinical setting. The present study was designed to simplify the interpretation of dipyridamole-thallium scans for preoperative cardiac risk assessment, all the while preserving the principle of correlating surgical risk with the amount of jeopardized myocardium.

METHODS

Patient group: The method was evaluated in a pilot study of 60 patients and then validated in a population of 355 patients. All patients were referred for dipyridamole-thallium imaging before vascular reconstruction or major nonvascular surgery. An adequate level of stress on the standard treadmill test could not be achieved either because of physical limitations or because of β-blocker usage. Patients who were referred for coronary revascularization before noncardiac surgery on the basis of the dipyridamole-thallium test were excluded from the study.

Dipyridamole infusion protocol: The dipyridamole infusion protocol is described in detail in a previous report.[13] Briefly, patients were studied in the fasting state, having avoided coffee, tea, soft drinks and chocolate for 24 hours, and all theophylline derivatives discontinued for 48 hours before the test. A no. 20 gauge cannula was inserted into a large antecubital vein and the cardiac rhythm continuously monitored with a II lead. Baseline and heart rate and blood pressure were recorded every minute. Dipyridamole was infused at a rate of 0.14 mg/kg/min over 4 minutes. After the infusion, the

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TABLE I Clinical Descriptors for the Pilot Study of 60 Patients

Clinical Parameter	No Event (n = 51)	Event (n = 9)	p Value
Age (years)	58.3 ± 10.7	63.1 ± 6.7	NS
No. of men	26 (51)	6 (66)	NS
Surgery			
Vascular	42 (82)	6 (66)	NS
Abdominal procedure	34 (66)	5 (55)	NS
Cerebrovascular disease	10 (19)	3 (33)	NS
Risk factors			
Mean number	1.63 ± 0.91	1.89 ± 0.99	NS
Cigarette smoking	42 (82)	7 (77)	NS
Systemic hypertension	21 (41)	4 (44)	NS
Diabetes mellitus	10 (19)	4 (44)	NS
Family history	8 (15)	0	NS
Angina grade			
0	24 (48)	7 (77)	NS
1	1 (2)	0	NS
2	12 (23)	1 (11)	NS
3	1 (2)	0	NS
Atypical chest pain	12 (23)	1 (11)	NS
Previous myocardial infarction	13 (25)	5 (55)	NS
Electrocardiogram			
Left ventricular hypertrophy	7 (13)	4 (44)	NS
ST-T	16 (31)	4 (44)	NS
Arrhythmia	5 (9)	4 (44)	NS

Angina grade = Canadian classification; Arrhythmia = any rhythm other than sinus or > 5 ventricular premature complexes per minute; ST-T = ST-T–segment abnormalities; NS = not significant.

patient stood up and walked in place for 2 minutes. At that point, 3.0 mCi of thallium-201 was injected as a compact bolus into the cannula rapidly followed by a 10 ml bolus of normal saline solution. The patient continued walking on the spot for 2 minutes, then lay under the scintillation camera and imaging was begun. During each study, 125 mg of aminophylline was available to reverse any serious adverse effects of dipyridamole. Patients who developed symptomatic myocardial ischemia responded quickly to intravenous aminophylline.

Thallium-201 myocardial imaging: The thallium imaging protocol, our definition of a fixed defect and the quantification method are described in detail in a previous report.[12] The first image was acquired in the best septal view, followed by the left anterior oblique 70° projection (with breast support in female patients), and the anterior view. Delayed images were obtained 4 hours after thallium injection and the patient was instructed to eat lightly during that time interval. Pre-set time 8-minute images were acquired in each of the 3 views (initial and delayed images) with a photopeak set at 80 kev with a 20% window. Care was taken to position the patients identically for the initial and redistribution studies. For each scintigraphic study, the following images were displayed: analog images, interpolated background subtracted images, circumferential profiles and washout rate analysis. All myocardial scintigraphic images were interpreted by 2 experienced observers without prior knowledge of patient history, coronary anatomy or postoperative outcome. Because of the high reported incidence of viable but "stunned" myocardium in fixed defects,[14] we usually injected 1 mCi of thallium before the rest images in patients with perfusion defects on the dipyridamole images, or occasionally acquired either delayed 24-hour resting thallium images or a radionuclide gated equilibrium ventriculogram (MUGA scan) under continuous intravenous nitroglycerin infusion to confirm the presence of scar tissue. Disagreements in interpretation were resolved by consensus.

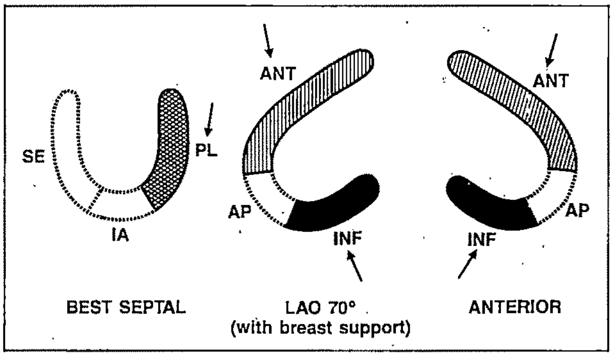

FIGURE 1. Anatomic regions on myocardial scans (total of 3 regions). The left ventricle was divided into 3 segments in each view, for a total of 9 segments. The 9 segments were condensed into 6 regions (anterior [ANT], apical [AP], inferior [INF], septal [SE], posterolateral [PL] and inferoapical [IA]), taking into account geometric overlap. When scintigraphic indexes for overlapping regions differed in magnitude, the segment with the most severe and reversible perfusion defect was considered as representative of the region. For the 3-segment model, only 3 regions are considered, the anterior, inferior and posterolateral segments *(arrows)*. LAO = left anterior oblique view.

Three-segment model: Scans were divided into segments (3 for each view), for a total of 9 segments. This was first simplified to 6 segments, taking into account anatomic overlap, and then to only 3 segments, ignoring the septal, inferoapical and true apical segments (empirically referred to as "minor segments"). Thus, the left ventricle was divided into anterior and inferior segments for the anterior and left anterior oblique 70° views, and the posterolateral segment for the best septal view. The final interpretation was based on only these segments (Figure 1).

Grading the severity of perfusion defects: All regional perfusion defects were graded according to a 3-point scale: grade 0/3, normal; grade 3/3, the most severe. Both immediate postdipyridamole and delayed (4-hour) images were evaluated.

Left ventricular cavitary dilation: The left ventricular cavity was measured in the best septal view on the immediate postdipyridamole and redistribution analog images. A patient was considered to show transient cavitary dilation when the cavity size on the early images was >15% larger than on the delayed images.

Study end points: Only cardiac death (acute myocardial infarction or sudden unexpected death) and acute myocardial infarction before discharge from the hospital were accepted as end points. Acute myocardial infarction was diagnosed when ≥2 of the following 3 criteria were met: (1) a recent episode of characteristic chest pain that lasted >30 minutes; (2) a transient increase above the upper limit of normal of total serum creatine kinase and its myocardial isoenzyme subfraction, related temporally to the episode of chest pain; and (3) Minnesota code criteria for definite or probable myocardial infarction accompanied by evolving ST- and T-wave changes.[15,16] The results of thallium studies

TABLE II Clinical Descriptors for the Validation Study of 355 Patients

	Coronary Event		
Clinical Parameter	Absent n = 325 (%)	Present n = 30 (%)	p Value
Age (years)	62.8 ± 10	67.5 ± 7	0.0130
No. of men	193 (59)	23 (77)	NS
Cerebrovascular disease	72 (22)	9 (30)	NS
Obstructive pulmonary disease			
None	244 (75)	16 (53)	
Mild	46 (14)	9 (30)	
Moderate	26 (8)	4 (14)	NS
Severe	8 (3)	1 (3)	
Renal failure	32 (10)	4 (13)	NS
History of CAD	181 (56)	24 (80)	0.01
Risk factors			
Number of risk factors	1.95 ± 1.02	2 ± 0.93	NS
Cigarette smoking	249 (77)	23 (77)	NS
Systemic hypertension	168 (52)	12 (40)	NS
Diabetes mellitus	63 (19)	14 (47)	0.0004
Family history	79 (24)	6 (20)	NS
Angina grade			
Asymptomatic	170 (52)	16 (53)	
1	25 (16)	1 (3)	
2	63 (41)	8 (27)	NS
3	10 (6)	0	
Atypical chest pain	57 (17)	5 (17)	
Unstable angina in previous 6 months	11 (3)	—	NS
Previous myocardial infarction	123 (28)	15 (50)	NS
History of CHF	18 (6)	5 (17)	0.024
Clinical CHF	6 (2)	2 (7)	NS
Electrocardiogram			
Left bundle branch block	9 (3)	2 (7)	NS
Left ventricular hypertrophy	45 (14)	7 (23)	NS
ST-segment abnormalities	128 (39)	17 (57)	NS
Arrhythmia	28 (9)	4 (14)	NS
Dipyridamole-thallium testing			
Chest pain	41 (13)	7 (23)	NS
Variations in heart rate	17.1 ± 11.2	14.93 ± 11.30	NS
Variations in blood pressure	18.9 ± 13.9	18.93 ± 9.80	NS

Angina grade = Canadian classification; CAD = coronary artery disease; CHF = congestive heart failure; NS = not significant; Renal failure = hemodialysis or renal transplant.

were made available to referring physicians and the decision to refer the patient for coronary angiography or directly to surgery was left to them. Patients with redistribution were usually monitored with a Swan-Ganz catheter during surgery, transferred to the intensive care unit after operation and followed by the consulting cardiologist postoperatively.

Statistical analysis: Correlation between clinical parameters, scoring systems, results of dipyridamole-thallium imaging, and cardiac events was done using chi-square analysis and analysis of variance. All values are mean ± standard deviation.

RESULTS

Pilot study of 60 patients: CLINICAL DESCRIPTORS: The clinical features of the 60 patients are listed in Table I.

SURGICAL PROCEDURES: A total of 48 patients underwent vascular surgery and 12 underwent major general surgery.

POSTOPERATIVE OUTCOME: There were 9 postoperative cardiac events: 7 coronary deaths (6 fatal myocardial infarctions and 1 sudden death) and 2 nonfatal myocardial infarctions. The events occurred an average of 3.9 days after surgery.

THALLIUM-201 IMAGING: SIX-SEGMENT MODEL: There were no postoperative events in 30 patients with normal perfusion in all 6 segments and without transient dipyridamole-induced cavitary dilation, and in the 9 patients with fixed defects. The cardiac event rate was 43% (9 of 21) in patients with reversible defects.

THALLIUM-201 IMAGING: "MINOR" SEGMENTS: There were 6 patients with perfusion defects confined to the apical, inferoapical and septal segments and none of these patients sustained a postoperative cardiac event.

THALLIUM-201 IMAGING: THREE-SEGMENT MODEL: Risk stratification using the 3-segment model was based on a stepwise approach. For purposes of clarity, patient subsets do not overlap. Step 1: There were 42 patients with normal anterior, inferior and posterolateral perfusion and without transient left ventricular dipyridamole-induced cavitary dilation. None of these patients developed postoperative cardiac complications. Step 2: (1) Among the remaining 18 patients, 1 patient with reversible defects in all 3 segments sustained a postoperative cardiac event. (2) Transient cavitary dilation was ob-

TABLE III Reversible Defects Confined to Minor Segments (n = 31)

Severity of reversible defects	
Grade 1/3	13 of 31
Grade 2/3	18 of 31
Extent of defects (no. of minor segments that displayed Tl-201 redistribution)	
1 segment	22 of 31
2 segments	8 of 31
3 segments	1 of 31
Location of defects*	
Septal	20 of 31
Inferoapical	12 of 31
Apical	9 of 31

*Total number > 31 because 9 of 31 patients had > 1 minor segment involved. Tl-201 = thallium-201.

served in 4 of the remaining 17 patients with a postoperative cardiac event rate of 75% (3 of 4). (3) At least 1 severe grade 3/3 reversible defect (absence of regional thallium uptake on the immediate postdipyridamole images and complete redistribution on delayed images) was observed in 2 of the remaining 13 patients and their postoperative cardiac event rate was 100%. Step 3: Among the remaining 11 patients, the cardiac event rate was 27% (3 of 11). The sample is too small to further stratify according to clinical parameters such as age.

Note that step 2 identifies 7 high-risk patients by scintigraphic criteria. These 7 patients comprise only 12% of the total patient population but account for 78% (7 of 9) of all postoperative cardiac events.

Validation study on 355 patients: The aforementioned stratification system based on 3 segments was validated on a group of 355 consecutive patients referred for cardiac risk assessment before noncardiac surgery including the 60 patients in the pilot study. Patients whose surgery was cancelled on the basis of results of the dipyridamole test or other factors were excluded.

CLINICAL DESCRIPTORS: The clinical features of the 355 patients are listed in Table II.

SURGICAL PROCEDURES: Vascular surgery: 66% (234 of 355). Elective aortic replacement for aortoiliac disease (73), resection of an abdominal (69) or thoracoabdominal (5) aortic aneurysm, ileofemoral and infrainguinal vascular reconstruction (63), aortic endarterectomy (1), aortorenal bypass (12), carotid surgery (9), splenorenal bypass (1).

Major general surgery: 14.6% (52 of 355). Esophageal, gastric and bowel surgery and various intraabdominal procedures (36), renal transplantation (7), neck dissection (8), mastectomy (1).

Urology: 3.7% (13 of 355). Nephrectomy (5), bladder surgery (4), radical prostatectomy (2), ureteral reconstruction (1).

Orthopedic surgery: 9% (32 of 355). Total hip (12) or knee (9) prosthesis, amputation (3), discoidectomy (7), hip arthroplasty (1).

Thoracic (lung) surgery: 3.9% (14 of 355).

Gynecologic surgery (hysterectomy or major vaginal surgery): 2.5% (9 of 355).

Neurosurgery for a brain tumor: 0.3% (1).

POSTOPERATIVE OUTCOME: There were 30 postoperative cardiac events: 19 coronary deaths (13 fatal myocardial infarctions and 6 sudden deaths) and 11 nonfatal myocardial infarctions. The events occurred an average of 4.1 days after surgery.

THALLIUM-201 IMAGING: SIX-SEGMENT MODEL: There was 1 fatal myocardial infarction and 1 nonfatal infarction in the 162 patients with normal perfusion in all 6 segments and without transient dipyridamole-induced cavitary dilation. The coronary death was a fatal anterior wall myocardial infarction 10 days after uneventful splenorenal bypass surgery and the coronary tree was normal at autopsy. There were no cardiac events in the 32 patients with only fixed defects as defined in this study. The cardiac event rate was 17.5% in 161 patients with reversible defects, including a 11.2% (18 of 161)

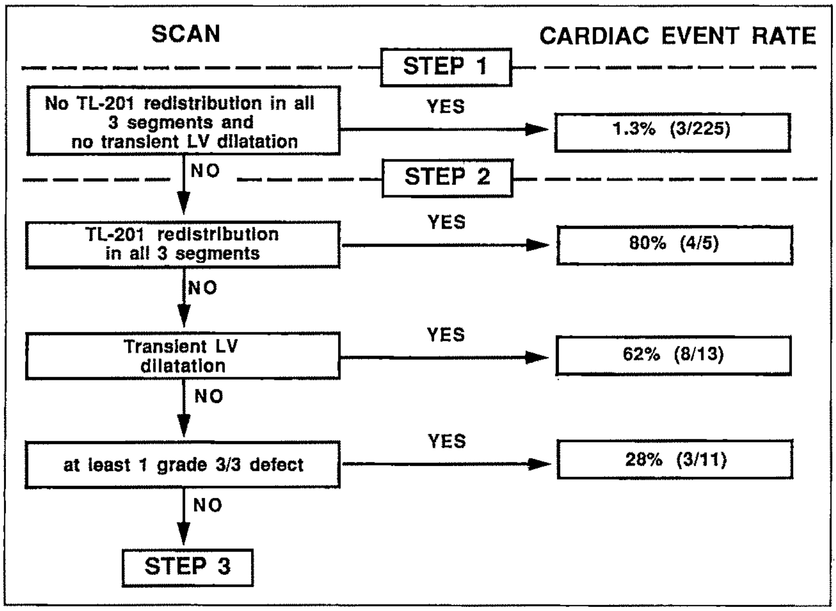
SCAN
CARDIAC EVENT RATE
STEP 1
No TL-201 redistribution in all 3 segments and no transient LV dilatation
YES
1.3% (3/225)
NO
STEP 2
TL-201 redistribution in all 3 segments
YES
80% (4/5)
NO
Transient LV dilatation
YES
62% (8/13)
NO
at least 1 grade 3/3 defect
YES
28% (3/11)
NO
STEP 3

FIGURE 2. Steps 1 and 2. All comments refer only to the 3-segment myocardial perfusion model. For purposes of clarity, patient subsets do not overlap. LV = left ventricular; TL = thallium.

cardiac death rate and a 6.2% (10 of 161) nonfatal infarction rate.

THALLIUM-201 IMAGING: MINOR SEGMENTS: There were 31 patients with perfusion defects confined to the apical, inferoapical and septal segments. The number, severity and location of the reversible defects are summarized in Table III. Only 1 of these patients (3%) sustained a postoperative cardiac event.

THALLIUM-201 IMAGING: THREE-SEGMENT MODEL: Risk stratification using the 3-segment model was based on a stepwise approach (Figures 2 and 3). For purposes of clarity, patient subsets do not overlap. Figure 2 illustrates steps 1 and 2. Step 1: There were 225 patients with normal anterior, inferior and posterolateral perfusion and without transient left ventricular dipyridamole-induced cavitary dilation. The postoperative cardiac event rate was 1.3% (3 of 225). Figure 2 illustrates steps 1 to 4. Step 2: (1) In the remaining 130 patients there were 5 patients with reversible defects in all 3 segments, with a postoperative cardiac event rate of 80% (4 of 5). (2) Transient cavitary dilation was observed in 13 of the remaining patients with a postoperative cardiac event rate of 62% (8 of 13) (3) At least 1 severe grade 3/3 reversible defect was observed in 11 of the remaining 125 patients with a postoperative cardiac event rate of 28% (3 of 11). (4) Stratification of the remaining 101 patients is based on the patient's age (age >70 years), presence of diabetes and the number of segments displaying reversible defects (1 or 2) (Figure 3).

DISCUSSION

Declining accuracy of dipyridamole testing: The sensitivity, specificity, positive and negative predictive accuracy of preoperative dipyridamole-thallium imaging interpreted conventionally as either positive (thallium redistribution) or negative are, respectively, 93% (28 of 30), 59% (192 of 325), 17.5% (28 of 161) and 99% (192 of 194) in this study. Interestingly, as dipyridamole-thallium imaging is being routinely performed preoperatively, its positive predictive accuracy (the likelihood that a patient with a positive scan will have a postoperative cardiac event) is gradually declining.[5,7] An early referral bias in favor of patients with more severe coronary artery disease is well illustrated by our own account of a 43% cardiac event rate in the early pilot study of 60 patients.[12]

The "risk" of preoperative cardiac risk assessment: Most investigators recommend preoperative coronary angiography in all patients with reversible defect(s) on dipyridamole-thallium scans.[1-10] Because the test was initially designed to screen for coronary artery disease, this would result in angiography performed and coronary revascularization being considered for most patients with coronary artery disease. By "risk" of cardiac risk assessment, we refer to the significant increase in total morbidity and mortality from widespread preoperative coronary arteriography and prophylactic revascularization being performed on the basis of a test with positive predictive accuracy of only 17.5%. Blombery et al[17] report a mortality rate as high as 2.4% from coronary arteriography alone in patients with multilevel vascular disease, and Hertzer et al[18] report an operative mortality in excess of 5% from prophylactic coronary revascularization before vascular reconstruction. In addition, the delay in performing noncardiac surgery increases the total risk to the patient (rupture of aortic aneurysm, acute limb ischemia).

Physiologic rationale for the three-segment system: By ignoring the apical and inferoapical segments, we eliminated the problem of an arbitrary cutoff between adjacent segments. The septum is a frequent source of interobserver variation of interpretation because there are numerous positional variants and because of breast-shielding artifacts. In addition, we assumed that life-threatening coronary disease would be unlikely to manifest itself solely as perfusion defects in distal/border zone coronary territories.

Step 1: rapid screen for low risk patients: The presence of thallium redistribution in the minor segments did not significantly alter the postoperative outcome:

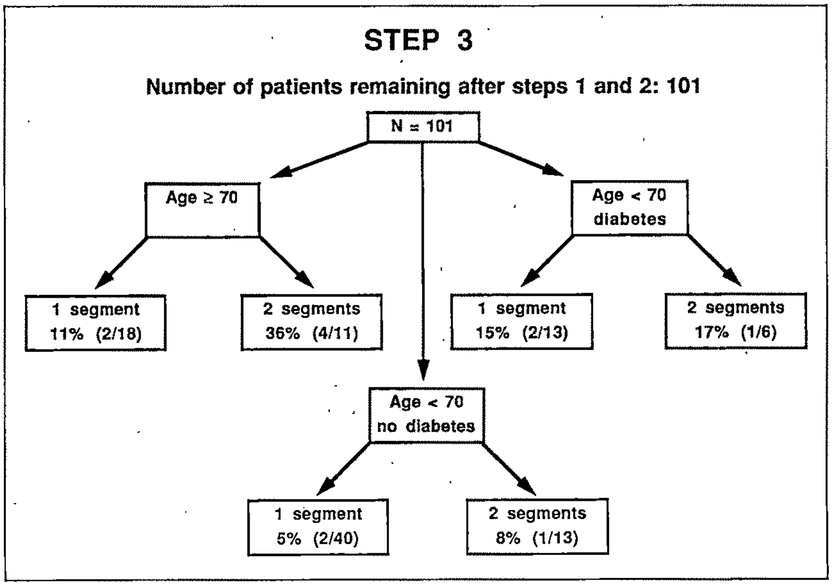

FIGURE 3. Step 3. Of the 355 patients in the study, 101 remain to be classified after steps 1 and 2. Patients are stratified according to age (≥70 years), presence of diabetes and number of segments involved (1 or 2). The cardiac event rate is shown for each subgroup.

only 1 of 31 patients (3%) with single or multiple perfusion defects limited to the 3 minor segments sustained a postoperative cardiac event (Table III).

Thus, 225 patients with normal anterior, inferior and posterolateral perfusion and without transient left ventricular dipyridamole-induced cavitary dilation comprised 63% of the total population (225 of 355), had an overall postoperative cardiac event rate of 1.3% (3 of 225), could be considered at low risk and referred directly to surgery (with antiischemic medication if there is thallium redistribution) (Figure 2).

Step 2: rapid screen for very high risk patients: The physiologic rationale consists of identifying patients who are most likely to have left main, 3-vessel or "high risk" 2-vessel coronary artery disease (including a proximal left anterior descending coronary artery stenosis) or a significant amount of jeopardized myocardium in the territory of a critical coronary stenosis. In a previous study, we showed that patients with transient dipyridamole-induced left ventricular cavitary dilation have severe underlying coronary artery disease, a high cardiac event rate after noncardiac surgery and a poor short-term prognosis.[19] In the present study, the small group of only 29 of 355 patients (8%) with either reversible defects of all 3 segments, transient cavitary dilation, or at least 1 severe grade 3/3 reversible defect, displayed a postoperative cardiac event rate of 52% (15 of 29), a clear indication that such patients should undergo preoperative coronary angiography.

In summary, with step 1, 63% of the patients (225 of 355) have been classified, whereas with step 2, 50% of complications (15 of 30) have been avoided.

Step 3: combining clinical and scintigraphic subsets: After steps 1 and 2, 101 patients remain to be stratified. The next stage in risk stratification is based on age ($p = 0.01$) and presence of diabetes ($p = 0.0004$) (Figure 3). After the age of 70 years, life expectancy and noncardiac mortality become prominent considerations and invasive cardiac testing becomes more dangerous. Diabetes is one of the few clinical parameters that consistently correlates with postoperative outcome in previous studies.[2]

Clinical implications: Before dipyridamole imaging, clinicians relied on the presence or absence of anginal symptoms or multivariate scoring systems for preoperative risk stratification. This approach lacked sensitivity and is associated with an increased postoperative cardiac complication rate. The introduction of dipyridamole imaging was greeted with enthusiasm because of the low event rate in patients with normal studies or fixed defects.[1-7] However, no distinction was made in interpreting the test for the diagnosis of coronary artery disease as opposed to risk stratification. Instead of missing high-risk patients, the problem was displaced, exposing large numbers of patients with coronary artery disease to the risk of systematic preoperative coronary angiography and prophylactic revascularization. The 3-step, 3-segment model is a clinically useful alternative to the conventional interpretation of the test for the purposes of quick and efficient preoperative risk stratification based on the rationale of correlating surgical risk with the amount of jeopardized myocardium. We are currently evaluating the prognostic value of this model to predict long-term survival.

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SYSTEMIC HYPERTENSION

Effects of Sustained-Release Nicardipine on Regression of Left Ventricular Hypertrophy in Systemic Hypertension

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The effects of a sustained-release formulation of the calcium antagonist nicardipine on left ventricular (LV) mass, Doppler transmitral velocity profiles and plasma neurohumoral studies were analyzed in patients with mild to moderate systemic hypertension. A double-blind placebo control phase in 28 patients was carried out for 6 weeks with a subgroup of 13 subsequently entering an open-label long-term phase for 1 year. Nicardipine produced a significant decrease in systolic and diastolic pressure over the 6-week phase (158 ± 15 to 142 ± 9 mm Hg, and 100 ± 5 to 89 ± 9 mm Hg, respectively, both $p < 0.001$). No significant differences in Doppler measures of mitral inflow or echocardiographic measures of LV function, wall thickness or mass were noted in the 6-week phase of the study. Although nicardipine increased both norepinephrine and renin values after the first dose, these levels had returned to baseline in most patients after 6 weeks. In addition, there was no evidence for stimulation of adrenomedullary activity because nicardipine had no effect on epinephrine or dopamine-B-hydroxylase levels at first dose or after 6 weeks.

In the 13 patients treated for 1 year, systolic and diastolic pressure remained significantly decreased compared with pressure before therapy (135 ± 9 vs 147 ± 15 mm Hg, and 85 ± 6 vs 97 ± 9 mm Hg, both $p < 0.01$). Concomitantly, both septal and posterior wall thickness decreased significantly (12.4 ± 1.5 to 10.7 ± 1.7 mm, and 11.0 ± 1.4 to 9.9 ± 1.7 mm, both $p < 0.02$) over 1 year as did LV mass index (150 ± 28 to 127 ± 31 g/m^2, $p < 0.02$). Importantly, no change was noted in LV cavity size, demonstrating that LV mass reduction was due solely to regression of hypertrophy. Doppler mitral inflow patterns were minimally affected with an increase in atrial velocity time integral. These results demonstrate that regression of LV hypertrophy takes place with long-term antihypertensive therapy with nicardipine, and this may be possible, in part, because of the lack of sustained neurohumoral stimulation by this agent.

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Systemic hypertension produces varying degrees of left ventricular (LV) hypertrophy, which is associated with increased cardiovascular morbidity and mortality.[1] In addition, diastolic dysfunction, determined by radionuclide angiography or Doppler echocardiography is often seen in these patients.[2–4] Diastolic dysfunction may precede LV hypertrophy and account for some early cardiac symptoms at a time when no systolic impairment is seen. Previous studies have documented regression of LV hypertrophy with various antihypertensive agents,[5,6] but accompanying improvement of diastolic dysfunction has not always been demonstrated.[7] The short-term effects of calcium antagonists on LV hypertrophy and diastolic dysfunction have been studied with variable results.[5,8] Little long-term data are available. Nicardipine, a calcium antagonist, with a high degree of selectivity for vasodilation if used long term may allow for baroreflex resetting with diminished neurohumoral cardiac stimulation.[9] This may permit regression of LV hypertrophy and improvement of diastolic dysfunction. Accordingly, we studied the short- and long-term effects of this drug on LV mass, Doppler-derived diastolic function and neurohumoral responses in patients with mild to moderate systemic hypertension.

METHODS

Patients: The study was performed at the University of California San Diego and Long Beach Veterans Affairs Medical Centers as part of a multicenter study conducted by Syntex, Inc. (Palo Alto, California) to evaluate the treatment of mild to moderate essential hypertension with a sustained release formulation of nicardipine. The study was approved by each institution's Human Subjects Institution Review Board and written consent was obtained. Forty-four patients with mild to moderate systemic hypertension were enrolled. After a 7-day washout, patients began treatment with a single blind regimen of placebo twice daily for 14 days. Only patients with supine diastolic blood pressure between 95 and 114 mm Hg on 2 visits continued. Of this group, 16

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were excluded because of diastolic blood pressure <95 (n = 7), noncompliance (n = 1), labile diabetes mellitus (n = 2), self-withdrawal (n = 5), and diastolic blood pressure >114 mm Hg (n = 1).

Twenty-eight patients qualified for the double-blind stage of the study. They were randomized to receive twice-daily placebo, or nicardipine twice daily, in 30, 45 or 60 mg doses.

Baseline studies included a complete history, physical examination, urinalysis, blood chemistries, hematology, electrocardiogram, Doppler echocardiography and plasma neurohumoral studies. After 6 weeks of treatment, patients returned for repeat Doppler echocardiography and plasma neurohumoral studies. Twenty-four of 28 patients completed the study (7 women, 17 men, age 57 ± 11 years, mean ± SD), the rest having withdrawn because of adverse events (n = 2), unsatisfactory therapeutic response (n = 1), and self-withdrawal (n = 1). The duration of treatment was 6.5 ± 0.6 weeks.

After repeat Doppler echocardiography and plasma studies at 6 weeks, the placebo group began therapy with a regimen of nicardipine, starting with 30 mg twice daily and titrating to 60 mg twice daily to achieve a diastolic blood pressure ≤ 90 mm Hg. The nicardipine group continued to take nicardipine, starting with 30 mg twice daily and titrating the dosage to the same blood pressure criteria. All patients had the option to continue taking the drug in a 1-year, open-label follow-up study with visits to monitor blood pressure, heart rate, compliance, and any adverse effects. Thirteen of 24 patients enrolled in and completed the study and returned at 1 year for repeat Doppler echocardiography (3 women and 10 men, age 61 ± 7 years), the rest having withdrawn because of adverse events, uncontrolled hypertension, noncompliance and self-withdrawal.

No patient had echocardiographic evidence of significant valvular disease at baseline. There was no known coronary artery disease or history of heart failure. One patient had non-insulin-dependent diabetes mellitus, 1 patient took thyroid replacement for hypothyroidism, and 1 patient required the addition of hydrochlorothiazide (25 mg daily) for additional control of hypertension during the last 5 months of the open-label study.

ECHOCARDIOGRAPHY: All patients were examined in the left lateral decubitus position at rest in quiet respiration. A Hewlett-Packard Sonos 500 (Andover, Massachusetts) was used for all echocardiographic studies. All recordings were saved on paper and video tape and later analyzed using an off-line ultrasound analysis system (Freeland Inc, Louisville, Colorado) by observers unaware of the study. Observers were unaware of treatment phase and reviewed study data among other studies from patients not enrolled in the project.

M-MODE ECHOCARDIOGRAPHY: A parasternal short-axis view was used and the tracing was recorded on paper. Following the recommendations of Sahn et al,[10] the following end-diastolic measurements were obtained: septal wall thickness (SEP), posterior wall thickness (PW), LV transverse diameter (LVTD), and LV cross-sectional area. The following calculations were carried out: fractional shortening = (LVTD at end-diastole − LVTD at end-systole)/end diastole. LV mass = $\{[(\text{SEP} + \text{PW} + \text{LVTD})^3 - (\text{LVTD})^3] \times 1.05\}/1{,}000$. LVMI (LVM index) = LVM/BSA, where BSA (total body surface area) = $[(\text{height} \times \text{weight})/3131]^{0.5}$.

SPECTRAL DOPPLER: An apical 4-chamber view was used and the sample volume placed between the mitral annulus and the tip of leaflets where there is maximal velocity with minimal spectral broadening. Care was taken to align the Doppler pulse to the direction of blood flow so as to minimize the angle between the 2. The tracings were recorded at either 50 or 100 mm/s on video tape and later replayed for analysis. At least 2 and up to 4 consecutive cycles were averaged. The curves were traced on a digitizer over the outer contour of the curves and measurements obtained on the off-line ultrasound analysis system for the following parameters: early deceleration time, PFV-E (peak flow velocity, early filling), PFV-A (peak flow velocity, atrial filling), velocity time integral, early, VTI-A (velocity time integral, atrial), and VTI-T (velocity time integral, total diastole). The following calculations were performed: (A/E-PFV) = (PFV-A)/(PFV-E); %A = (VTI-A)/(VTI-T); peak flow rate, early = (PFV-E)/(VTI-T); and peak flow rate-atrial = (PFV-A)/(VTI-T). (This formula was used for normalized peak flow rate because it eliminates the need to estimate the actual annular area, which varies throughout diastole.[11])

Neurohumoral analysis: PLASMA STUDIES: All patients had blood sampled for norepinephrine, epinephrine, renin and aldosterone. Studies were performed at the end of the single-blind (placebo) phase, 3 hours after the first dose of nicardipine and after 6 weeks of therapy 12 hours after the last dose of sustained release nicardipine to measure the acute and chronic response to the drug. After an overnight fast, subjects had a heparin lock inserted into an antecubital vein and thereafter they rested in the recumbent position for 20 minutes at which time blood samples were taken for norepinephrine, renin and aldosterone.

ASSAYS: Samples for renin and aldosterone were collected separately in iced tubes containing ethylenediaminetetraacetate. Plasmas were separated within 30 minutes and were frozen at −70°C until assayed. Plasma renin activity was determined by radioimmunoassay.[12] Aldosterone was measured by radioimmunoassay kit form supplied by Diagnostic Products. (Aldosterone Cot-A-Kit model TKAL-1, Diagnostic Products, Los Angeles, California). Samples for norepinephrine and epinephrine were collected in iced, heparinized tubes and the plasma was separated within 30 minutes. Samples were stored at −70°C until assayed. Catecholamines were measured by the catechol-o-methyltransferase-based radioenzymatic technique of Ziegler et al.[13] The technique has an intraassay coefficient of variation of 6%.

STATISTICAL ANALYSIS: Results are expressed as mean ± standard deviation. Comparisons were made using paired and unpaired *t* tests. Significance was defined as a p value <0.05 for single comparisons and 0.02 when ≥ 2 comparisons were made (i.e., baseline, 6-week and 1-year).

Intraobserver variability analysis was performed by examining the same cardiac cycles for 16 patients on 2 occasions 2 weeks apart.

RESULTS

Effect of nicardipine treatment: BLOOD PRESSURE AND HEART RATE: The baseline blood pressure for the nicardipine group (n = 17; 158 ± 15/100 ± 5 mm Hg) was mildly but significantly ($p < 0.05$) greater than the baseline level for the placebo group (n = 7; 145 ± 5/96 ± 1 mm Hg). Systolic and diastolic blood pressure decreased significantly in the nicardipine group at 6 weeks (142 ± 9/89 ± 9 mm Hg, $p < 0.001$), whereas no significant changes occurred in the placebo group (147 ± 14/93 ± 7 mm Hg). After 1 year, both the systolic and diastolic blood pressure remained low compared with initial values (n = 13; 147 ± 15/97 ± 9 mm Hg at baseline vs 138 ± 10/86 ± 8 mm Hg at 6 weeks, p <0.01 vs 135 ± 9/85 ± 6 mm Hg at 1 year, $p < 0.01$). Heart rate did not change in any group at 6 weeks or at 1 year (70 ± 9, 70 ± 12, 71 ± 9 beats/min for baseline, 6 weeks and 1 year, respectively, p = not significant [NS]).

M-MODE ECHOCARDIOGRAPHY: Technically adequate studies were obtained in 22 of 24 patients in the 6-week trial and in 9 of 13 patients at 1 year. In comparing the groups at entry (nicardipine or placebo), LV mass index was slightly but not significantly greater in the nicardipine subgroup at baseline. At 6 weeks, no significant changes had taken place in any of the echocardiographic measurements in either group (Table I). The subgroup treated for 1 year did, at baseline, have significantly greater septal and posterior wall thickness as well as LV mass and mass index values than the placebo group at entry. However, in the subgroup followed for 1 year, significant decreases were found in both septal and posterior wall thickness, LV mass and LV mass index. Importantly, no change was noted in LV chamber dimension, thereby demonstrating that LV mass reduction was due to regression of hypertrophy, not reduction of LV cavity size.

SPECTRAL DOPPLER: Technically adequate studies were obtained in 23 of 24 patients in the 6-week trial and in 12 of 13 at 1 year. No significant baseline differences existed for Doppler variables between subgroups. No differences were found in any of the parameters measured in either group at 6 weeks or in the subgroup after 1 year except for the percent of atrial contribution to filling which increased significantly (Table II).

INTRAOBSERVER VARIABILITY: Intraobserver variability determined for both Doppler and M-mode echocardiographic variables ranged from 2.7% for peak filling velocity of the A wave to 10.7% for deceleration time of E wave. The variability for posterior and septal wall thickness was 6.6 and 6.9%, respectively.

Neurohumoral analysis: Placebo and the lowest dose of nicardipine had no significant effect on baseline norepinephrine, renin or aldosterone levels. Forty-five and 60 mg doses increased both norepinephrine and renin levels after the first dose. After 6 weeks of nicardipine therapy, norepinephrine levels returned to baseline and

TABLE I Echocardiographic Variables at Baseline, Six Weeks and One Year in Placebo and Treatment Subgroups

	Placebo (n = 7)			Nicardipine (n = 17)			Long-Term Nicardipine (n = 9)					
Left Ventricle	Before Therapy	Pre-tx vs 6 Weeks	6 Weeks	Before Therapy	Pre-tx vs 6 Weeks	6 Weeks	Before Therapy	Pre-tx vs 6 Weeks	6 Weeks	6 Weeks vs 1 Year	1 Year	Pre-tx vs 1 Year
Septal wall thickness (mm)	9.9 ± 1.3	NS	9.7 ± 1.6	10.6 ± 2.3	NS	10.2 ± 2.1	12.4 ± 1.5*	NS	11.7 ± 2.1	NS	10.7 ± 1.7	0.02
Posterior wall thickness (mm)	9.3 ± 0.7	NS	8.9 ± 1.2	9.9 ± 2.0	NS	9.6 ± 1.7	11.0 ± 1.4*	NS	10.6 ± 1.4	NS	9.9 ± 1.7	0.02
End-diastolic diameter (mm)	50 ± 4	NS	51 ± 4	51 ± 4	NS	52 ± 5	52 ± 5	NS	53 ± 5	NS	52 ± 6	NS
Fractional shortening (%)	42 ± 7	NS	41 ± 7	41 ± 8	NS	40 ± 6	46 ± 10	NS	40 ± 7	NS	40 ± 6	NS
Cross-sectional area (cm2)	18 ± 3	NS	18 ± 3	18 ± 4	NS	19 ± 5	22 ± 3	NS	23 ± 4	NS	21 ± 5	NS
Mass (g)	220 ± 48	NS	219 ± 46	251 ± 84	NS	253 ± 85	307 ± 73*	NS	298 ± 74	0.02	260 ± 78	0.02
Mass index (g/m^2)	111 ± 20	NS	111 ± 22	124 ± 38	NS	124 ± 38	150 ± 28*	NS	150 ± 28	0.02	127 ± 31	0.02

*$p < 0.01$ long-term versus placebo pretherapy.
NS = not significant; Pre-tx = before therapy

TABLE II Doppler Variables at Baseline, Six Weeks and One Year in Placebo and Treatment Subgroups

	Placebo (n = 7)			Nicardipine (n = 16)			Long-Term Nicardipine (n = 12)					
Mitral Inflow	Before Therapy	Pre-tx vs 6 Weeks	6 Weeks	Before Therapy	Pre-tx vs 6 Weeks	6 Weeks	Before Therapy	Pre-tx vs 6 Weeks	6 Weeks	6 Weeks vs 1 Year	1 Year	Pre-tx vs 1 Year
Deceleration time-E (s)	0.18 ± 0.05	NS	0.17 ± 0.05	0.18 ± 0.04	NS	0.18 ± 0.05	0.17 ± 0.04	NS	0.17 ± 0.05	NS	0.13 ± 0.03	NS
Peak flow velocity-E (cm/s)	0.7 ± 0.1	NS	0.7 ± 0.1	0.7 ± 0.1	NS	0.6 ± 0.1	0.6 ± 0.1	NS	0.6 ± 0.2	NS	0.6 ± 0.1	NS
Peak flow velocity-A (cm/s)	0.7 ± 0.1	NS	0.7 ± 0.1	0.6 ± 0.2	NS	0.7 ± 0.2	0.6 ± 0.2	NS	0.7 ± 0.2	NS	0.6 ± 0.1	NS
Peak flow velocity-A/E	0.96 ± 0.2	NS	1.02 ± 0.2	1.09 ± 0.3	NS	1.13 ± 0.3	0.99 ± 0.25	NS	1.09 ± 0.3	NS	1.11 ± 0.2	NS
Peak flow rate-E (s)	3.5 ± 0.5	NS	3.5 ± 0.6	3.2 ± 0.8	NS	3.3 ± 0.7	3.4 ± 0.6	NS	3.4 ± 0.6	NS	3.1 ± 0.3	NS
Peak flow rate-A (s)	3.4 ± 0.6	NS	3.6 ± 0.8	3.4 ± 0.8	NS	3.7 ± 0.9	3.3 ± 1.0	NS	3.7 ± 1.2	NS	3.5 ± 0.7	NS
Velocity time integral-E (m)	0.11 ± 0.11	NS	0.11 ± 0.02	0.11 ± 0.02	NS	0.10 ± 0.03	0.11 ± 0.02	NS	0.10 ± 0.03	NS	0.10 ± 0.03	NS
Velocity time integral-A (m)	0.07 ± 0.01	NS	0.08 ± 0.02	0.08 ± 0.02	NS	0.08 ± 0.02	0.08 ± 0.02	NS	0.08 ± 0.02	NS	0.09 ± 0.02	NS
% A	37 ± 8	NS	41 ± 11	43 ± 7	NS	43 ± 7	41 ± 8	NS	42 ± 10	NS	50 ± 10	0.01

Abbreviations as in Table I.

renin activity remained elevated only at the 45 mg dose (Figure 1). Renin activity leads to aldosterone release. Although there was a trend for aldosterone to increase with higher nicardipine doses, the increase generally did not reach statistical significance (Figure 1).

Sympathetic nerves release norepinephrine and dopamine-B-hydroxylase, while the adrenal medulla releases norepinephrine, epinephrine and dopamine-B-hydroxylase. There was no evidence for stimulation of adrenomedullary activity. Specifically, nicardipine had no effect on plasma epinephrine; the basal epinephrine value of 26 pg/ml changed by −4 ± 6 with placebo, and by −2 ± 7, 0 ± 6 and 7 ± 6 pg/ml after the first dose of 30, 45 and 60 mg of nicardipine, respectively (all p = NS). After 6 weeks, there was a change from basal epinephrine of 1 ± 5 after placebo and 0 ± 6, −7 ± 5 and 5 ± 6 pg/ml for 30, 45 and 60 mg of nicardipine, respectively (all p = NS). Similarly, no significant change in dopamine-B-hydroxylase levels at first dose or at 6 weeks were noted. The change in basal values with placebo was 62 ± 89 and 61 ± 91 nm/ml/hour at first dose and after 6 weeks, (all p = NS), respectively, whereas the change with nicardipine in 30, 45 and 60 mg doses was 122 ± 98, 113 ± 89 and −28 ± 92, respectively, for first dose, and 16 ± 102, 47 ± 88 and −36 ± 103, respectively, at 6 weeks (all p = NS).

DISCUSSION

Nicardipine reduces systemic hypertension and long-term use of the drug decreases LV mass. This finding is consistent with a previous study that demonstrated reduction of LV mass with another calcium channel antagonist after 6 months of therapy.[5] Further, in the current study, the reduction in LV mass was due to a reduction in wall thickness and not the end-diastolic dimension of the left ventricle, which remained unchanged over 1 year. The reduction in wall thickness was demonstrated in a subgroup who had significantly greater LV mass and wall thickness at baseline than the initial placebo and nicardipine subgroups of the trial. This difference among subgroups was coincidental in that all patients were given the opportunity to enroll in the chronic phase of the study and the investigators who followed patients, as well as the patients themselves, were unaware at all times of echocardiographic results. This coincidence is fortuitous in some respects in that it demonstrates that the drug produced regression of LV hypertrophy in patients with the most pronounced hypertrophy.

There was an acute increase in plasma norepinephrine levels which did not persist. Renin levels were only variably increased and the drug had no measurable effect on epinephrine or dopamine-B-hydroxylase and little effect on aldosterone levels. Nicardipine had only small or transient effects on the sympathetic nervous system and the renin-aldosterone system. Norepinephrine increases peripheral vascular resistance and directly stimulates the myocardium. The eventual return of norepinephrine to basal levels in patients being treated with nicardipine may permit the regression of cardiac hypertrophy.

Other studies with calcium antagonists have shown variable results with respect to acute and chronic effects on renin, aldosterone and catecholamines in patients with systemic hypertension. One study involving nifedipine demonstrated a similar acute stimulation of catecholamines with a return to normal of these values as well as aldosterone at 6 weeks but with a persistent decline in systemic blood pressure.[14] However, Katzman et al,[15] studying felodipine in essential hypertension, found that norepinephrine and plasma renin activity were persistently elevated after 10 weeks of therapy when compared with pretreatment levels. These changes were seen in the setting of reduced systemic blood pressure and unchanged heart rate. Unfortunately, no data concerning regression of LV mass with long-term therapy were reported.

This study did not demonstrate improvement in the abnormal Doppler-derived indexes of diastolic dysfunction. On the contrary, the percentage of atrial (velocity time integral) contribution to filling, which was relatively high before therapy, increased further, a finding opposite to that expected if this drug were to improve diastolic filling because of regression of LV hypertrophy. Several potential explanations exist for the disparity in these findings compared with previous studies. The ratio of early to late diastolic filling as measured by Doppler indexes is dependent on heart rate, the transmitral pressure difference, atrioventricular conduction time, preload, age, and possibly on LV mass.[16-18] Although no heart rate changes were seen in our patients, it is possible this was not the case in other studies using agents such as β-blockers or other calcium antagonists that are known to alter heart rate or atrioventricular conduction time. Preload determines the late to early filling ratio as measured by Doppler[19] and may have been affected in these patients by the vasodilator properties of nicardipine. However, no difference in end-diastolic dimensions of the left ventricle was seen, which suggests that loading conditions were not dissimilar before and after treatment.

Another possible explanation for the failure of these diastolic profiles to improve is suggested by work from Krayenbuehl and co-workers,[20] who evaluated myocardial function and structure long term after aortic valve replacement for aortic stenosis and regurgitation. Persistence of increased interstitial fibrous content was seen despite regression of myocardial cellular hypertrophy in these patients. It is possible that this same relative inter-

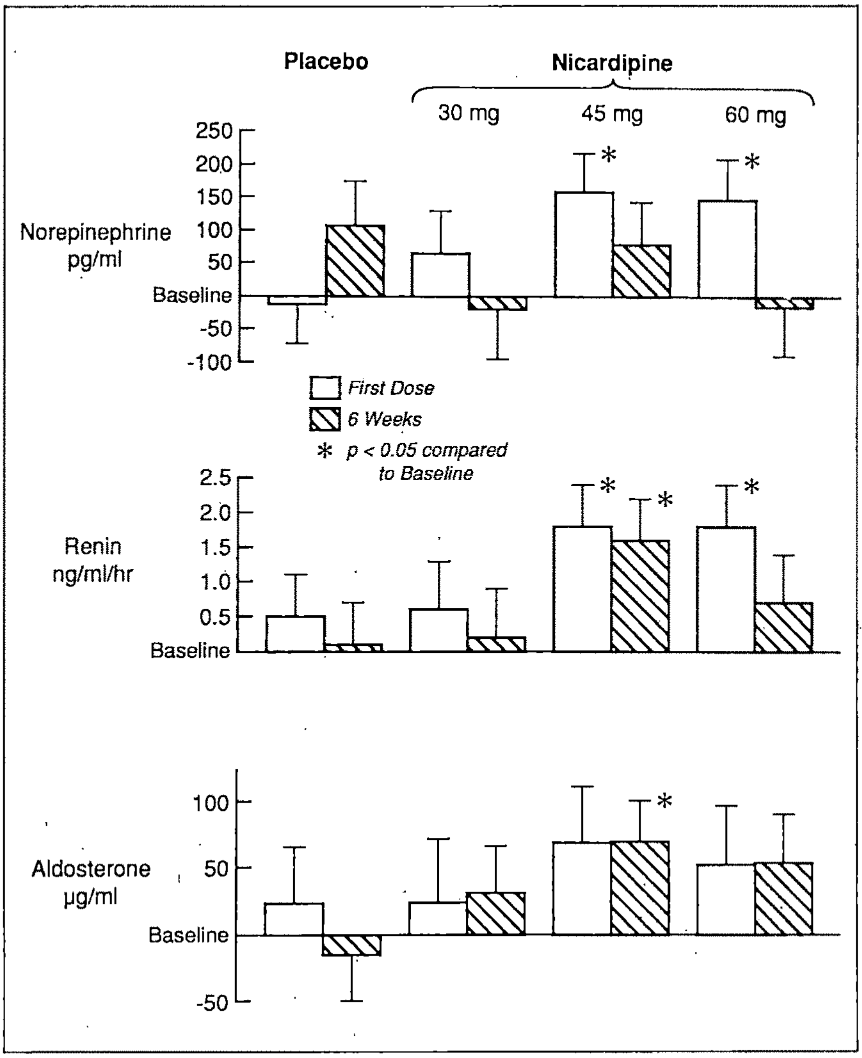

FIGURE 1. Effect of placebo and nicardipine at multiple doses on baseline norepinephrine, renin and aldosterone levels after first dose and at 6 weeks. The norepinephrine and renin levels increase after the first dose of nicardipine, but for the most part return to baseline at 6 weeks. Little effect on baseline aldosterone levels is noted.

stitial fibrosis exists in the current population at 1 year and accounts for the lack of improved Doppler diastolic indexes.

Shahi et al[7] demonstrated regression of LV hypertrophy in hypertensive patients treated with an angiotensin-converting enzyme inhibitor without concomitant improvement in Doppler derived indexes of diastolic function. Also, Pasierski et al[21] recently demonstrated that the altered patterns of mitral inflow in hypertensive subjects, particularly peak velocities and velocity time integrals, were not related to systemic arterial pressure or to altered LV geometry including mass. However, they did demonstrate that age and heart rate were important determinants of velocity profiles and suggested that the abnormal filling in hypertensive patients is most likely secondary to abnormal myocardial relaxation. Thomas and Weyman,[22] in an elegant discussion of Doppler mitral inflow patterns, pointed out that although important physiologic information is contained within these profiles, the patterns are not equivalent to diastolic function. It is therefore difficult to make inferences concerning changes in these patterns in the clinical setting.

Only half of the initial population completed the long-term portion of the study and as previously noted, the subgroup treated for 1 year had significantly greater hypertrophy at baseline. Despite this, echocardiographic results documented a clear-cut reduction in LV mass because of a decrease in wall thickness. In addition, this reduction in wall thickness was substantially greater than the intraobserver variability for these measurements.

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Anaerobic Threshold Detection in Patients with Congestive Heart Failure

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Anaerobic threshold measurements determined either invasively by analysis of arterial lactate concentration (lactate threshold) or noninvasively by respiratory gas exchange analysis (ventilatory threshold) were compared in patients with chronic congestive heart failure. Sixteen patients performed symptom-limited maximal exercise on a bicycle ergometer using a continuous ramp protocol with measurement of arterial lactate concentration at 1 minute intervals, and continuous breath-by-breath analysis of respiratory gas exchange. A specific lactate threshold point was detected in only 7 patients. These 7 patients had significantly greater peak oxygen uptake than did the 9 in whom no specific lactate threshold point was detected (15.9 ± 1.0 vs 10.5 ± 0.5 ml/kg/min; p <0.05). Ventilatory threshold significantly correlated with lactate threshold in these 7 patients. In the remaining 9 patients, neither lactate nor ventilatory threshold could be reliably determined with methods used in the present study.

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Maximal oxygen uptake (VO_2) is difficult to determine in many patients with severe congestive heart failure (CHF) who do not reliably reach a plateau in VO_2 during symptom-limited maximal exercise.[1] Anaerobic threshold has been proposed as an alternative objective measure of submaximal exercise capacity in this group of patients.[2] Anaerobic threshold can be determined either invasively by analysis of arterial lactate concentration (lactate threshold) or noninvasively by respiratory gas exchange analysis (ventilatory threshold).[3,4] The clinical use of anaerobic threshold determination in CHF has been limited by the absence of a consensus on the best methodology for lactate and ventilatory threshold detection.[5-9] Furthermore, reported methods are subject to substantial intra- and interobserver variability, because anaerobic threshold determination is based on subjective interpretation of lactate or gas exchange data.[10,11] Recent refinements in exercise protocols and gas exchange analysis systems, and more objective techniques of anaerobic threshold detection have increased the precision and reproducibility for both lactate and ventilatory thresholds in normal human subjects.[12,13] Accordingly, the present study was performed to evaluate these new methods in patients with CHF.

METHODS

Patients: Fourteen men and 2 women (mean age 60 years, range 48 to 69) with stable CHF in New York Heart Association class II or III were studied. The etiology of CHF was coronary artery disease in 4 patients, idiopathic dilated cardiomyopathy in 10, and hypertensive heart disease in 2. Left ventricular ejection fraction (as determined by radionuclide angiography within 6 months of the study) averaged 25% (range 15 to 33). All patients were treated with stable doses of digoxin, diuretics and an angiotensin-converting enzyme inhibitor. Cardiac medications were withheld on the morning of the study. By the criteria proposed by Weber et al,[14] 4 patients were class B (peak VO_2 16.7 to 19.4 ml/kg/min), 8 were class C (10.3 to 14.4 ml/kg/min), and 4 were class D (9 to 9.9 ml/kg/min). Patients with exercise-induced myocardial ischemia, peripheral vascular disease (ankle/arm blood pressure ratio <1) or obstructive lung disease (forced expiratory volume at 1 second/forced vital capacity <70%) were excluded from the study.

Exercise protocol: All patients performed bicycle ergometry with respiratory gas exchange monitoring before the study to ensure familiarization with the exercise equipment. Patients were studied in the morning after an overnight fast. Before exercise, a 20-gauge polyethylene catheter was placed in the radial artery. Patients

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performed a symptom-limited maximal exercise test on an electronically braked cycle ergometer (Mijnhardt Model KEM III) using a continuous ramp protocol. After resting for 2 minutes on the bicycle, patients pedaled at approximately 60 rpm as the work load increased from 0 W at a rate of 5 to 10 W/min, adjusted to patient's previous exercise performance to maintain the duration of the test between 8 and 12 minutes. Arterial lactate samples were collected at rest, at 1-minute intervals during exercise, and at 1 and 3 minutes after exercise. Blood samples were immediately deproteinized with iced perchloric acid for later analysis. Expired gases were collected through a low-resistance 3-way valve (Hans Rudolph) for 1 to 2 minutes at rest, and continuously during exercise. VO_2, carbon dioxide production (VCO_2) and minute ventilation were continuously monitored on a breath-by-breath basis (Medical Graphics 2001). Because no plateau in VO_2 at end-exercise was observed in patients, peak VO_2 was defined as the average value of VO_2 in the last 30 seconds of exercise when the respiratory exchange ratio was >1.05.

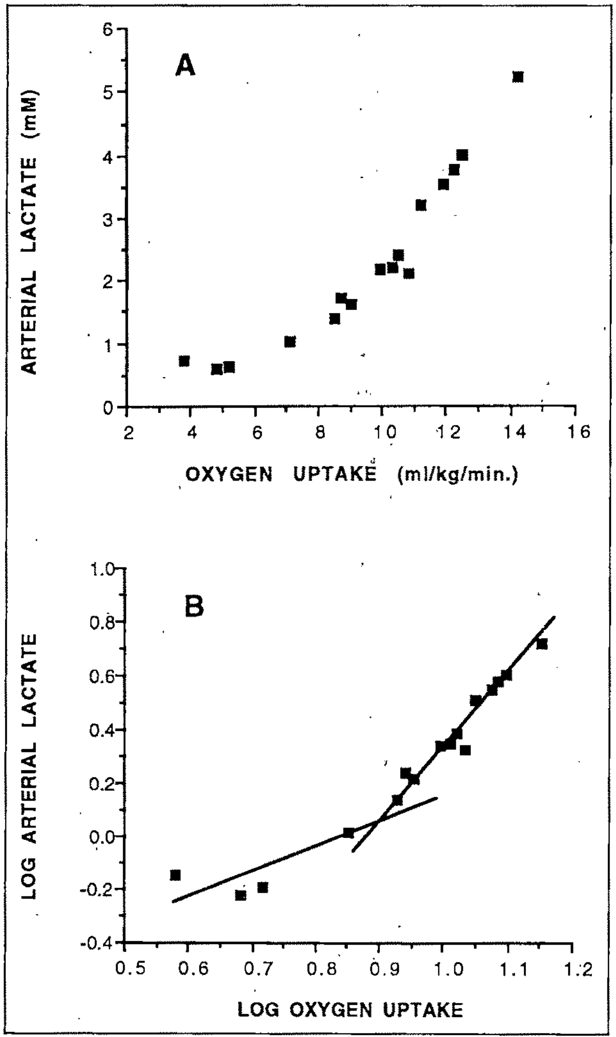

FIGURE 1. Representative plots in patient with detectable lactate threshold. *A*, plot of oxygen uptake versus arterial lactate concentration is curvilinear without clear threshold point. *B*, log-log transformation of data demonstrating lactate threshold. *Lines* shown derived from linear regression analysis of first 5 and last 12 data points. *Intersection of lines* marks lactate threshold.

Determination of anaerobic threshold: Anaerobic threshold was determined by both arterial blood lactate concentrations (lactate threshold) and analysis of expired gases (ventilatory threshold).

LACTATE THRESHOLD: Arterial blood lactate concentration was determined by a spectrophotometric method in mmol/liter (Sigma Kit). Lactate threshold was determined by the following 2 methods: (1) visual inspection of the plot of arterial lactate concentrations versus VO_2, and (2) log-log transformation of the lactate and VO_2 data, as described by Beaver et al.[12] A sharp inflection point, if present, was chosen by visual inspection, and lactate threshold was determined by a 2-segment linear regression model.

VENTILATORY THRESHOLD: Ventilatory threshold was determined by both subjective interpretation of respiratory gas exchange data (VT standard) and by a computerized method (VT-$\dot{V}$ slope).

VT standard was determined independently by 2 investigators familiar with the criteria for anaerobic threshold detection, as described by Wasserman.[15] VO_2, VCO_2, minute ventilation, respiratory exchange ratio (R), ventilatory equivalents of VO_2 and VCO_2 (VE/VO_2 and VE/VCO_2, respectively), and end-tidal partial pressures of oxygen and carbon dioxide (P_{et} O_2 and P_{et} CO_2, respectively) were plotted versus time, using an 8-breath moving average filter. Ventilatory threshold was considered present when: (1) the $VE/\dot{V}O_2$ curve reached a minimum and began to rise, while the VE/VCO_2 curve remained flat, (2) the P_{et} O_2 curve began to rise, while the P_{et} CO_2 curve remained flat, and (3) the slope of the R curve began to rise more sharply during exercise. Ventilatory threshold was chosen from the plot that most clearly satisfied Wasserman's criteria. Values for ventilatory threshold determined independently by each observer were highly correlated ($r = 0.92$, $p < 0.01$) and varied from each other by ≤10% in any patient. The average of the values found by the 2 observers was reported as the VT standard.

Ventilatory threshold was determined with the computerized V-slope method described by Beaver et al,[13] with a software program supplied by Medical Graphics. This method (based on a 2- or 3-segment linear regression analysis of the plot of VO_2 vs VCO_2) was previously demonstrated to be superior to standard plots for detection of ventilatory threshold in normal subjects. Resting ventilatory data and those from the first minute of exercise were excluded from the computer analysis owing to nonlinear kinetics of gas exchange at the beginning of exercise.

Time values for ventilatory threshold chosen by either method were rounded to the nearest 15-second interval, and VO_2 was determined from a computer-averaged 15-second interval report.

Data analysis: All values are stated as mean ± SD. Patients with and without detectable ventilatory threshold were compared using Student's unpaired *t* test. Different methods of anaerobic threshold detection were compared using 1-way analysis of variance with the

Scheffe test for post hoc determination of statistical significance. Single linear regression analysis was also performed using the least-squares method. Statistical significance was accepted at the 95% confidence limit (2-tailed p value <0.05).

RESULTS

Lactate threshold: Arterial lactate concentration increased curvilinearly as a function of VO_2 in 7 patients in whom a clear threshold point was detected by a log-log transformation of the data (Figure 1). Arterial lactate increased linearly as a function of VO_2 in 9 patients in whom no clear lactate threshold could be detected even with a log-log transformation of the data (Figure 2).

Peak VO_2 was significantly lower in patients without detectable lactate threshold than in those in whom lactate threshold was present (Table I). A specific lactate threshold point was not detected in any patient with severe CHF (peak VO_2 <12 ml/kg/min), but was present in all with mild to moderate CHF (>14 ml/kg/min). For patients with peak VO_2 between 12 and 14 ml/kg/min, lactate threshold was detected in 2 and not detected in 1. Arterial lactate concentrations at rest and after 2 minutes of exercise (corresponding to a work load of 10 to 20 W), and percentage of peak VO_2 after 2 minutes of exercise were significantly greater in patients without detectable lactate threshold.

Ventilatory threshold (Table II): Ventilatory threshold was detected from examination of standard plots in 12 patients and by the computerized V-slope method in 14. Ventilatory threshold was detected by both methods in the 7 patients in whom lactate threshold was present. In 9 patients without detectable lactate threshold, ventilatory threshold was determined by standard plots in 5 and by the V-slope method in 7. In the remaining patients, no clear threshold point was evident on plots of respiratory gas exchange.

Comparison of methods: Lactate threshold (when detected) significantly correlated with both VT standard (r = 0.79, p <0.05) and VT-V slope (r = 0.78, p <0.05; Figure 3). Lactate threshold occurred at a significantly lower VO_2 and arterial lactate concentration than did ventilatory anaerobic threshold determined by standard plots or the V-slope method (p <0.05; Table II and Figure 4). VT-V slope tended to occur earlier in exercise than did VT standard and was closer to the lactate threshold.

DISCUSSION

In patients with severe CHF (peak VO_2 <12 ml/kg/min), lactate threshold could not be detected with the methods used in this study. In patients with mild to moderate CHF (peak VO_2 >14 ml/kg/min), ventilatory threshold determined by analysis of gas exchange data was closely related to the lactate threshold.

Our findings in patients with severe CHF are in agreement with previous reports. Weber and Janicki[5] described a rapid linear increase in blood lactate concentration in patients with severe aerobic impairment (peak VO_2 <10 ml/kg/min). Wilson et al[6] reported a rapid early increase in lactate concentration in 15 of 48 patients studied when exercise capacity was <6 minutes, corresponding to a peak work load of <60 W on a cycle ergometer. Simonton et al,[7] Matsumura et al[8] and

TABLE I Clinical Characteristics of Patients With and Without Detectable Lactate Threshold

	Lactate Threshold Present	Lactate Threshold Absent	p Value
Age (yr)	58 ± 6	62 ± 8	NS
Left ventricular ejection fraction (%)	23 ± 7	25 ± 8	NS
Exercise duration (sec)	663 ± 126	541 ± 156	NS
Peak VO_2 (ml/kg/min)	15.9 ± 2.7	10.5 ± 1.4	<0.001
Peak work rate (W)	95 ± 18	54 ± 16	<0.01
Resting lactate (mmol)	0.8 ± 0.2	1.0 ± 0.3	<0.05
Lactate at 2 minutes of exercise (mmol)	1.0 ± 0.3	1.5 ± 0.4	<0.05
% peak VO_2 at 2 minutes of exercise	53 ± 6	77 ± 9	<0.05

NS = not significant; VO_2 = oxygen uptake.

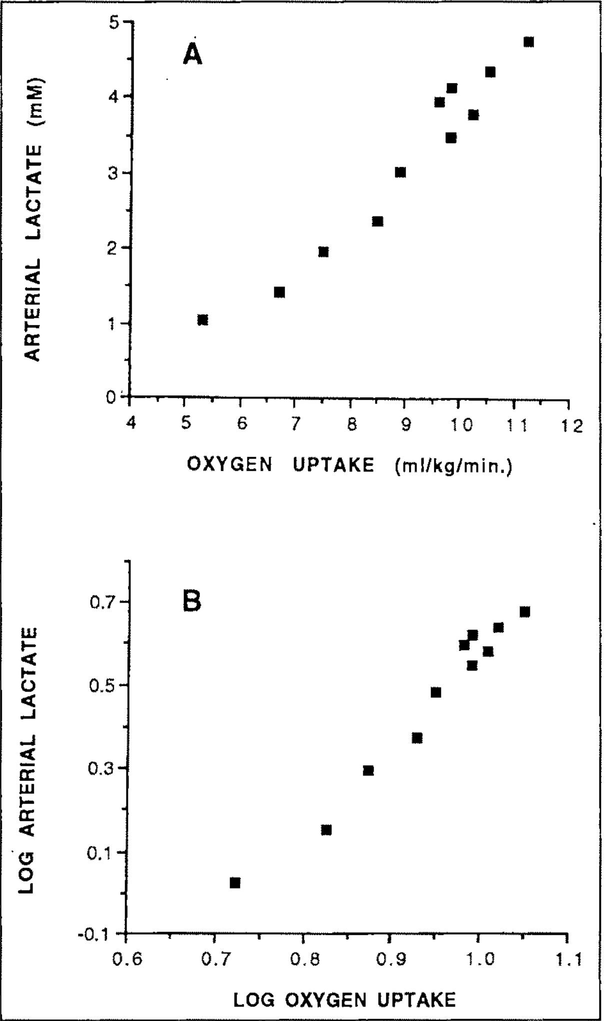

FIGURE 2. Representative plots in patient without detectable lactate threshold. *A*, plot of oxygen uptake versus arterial lactate concentration increases linearly from onset of exercise. *B*, log-log transformation of data reveals no threshold point.

TABLE II Comparison of Methods for Detection of Anaerobic Threshold

			Lactate Threshold		VT-V Slope		VT Standard	
Pt.	Peak VO_2	Peak Lactate	VO_2	Lactate	VO_2	Lactate	VO_2	Lactate
Lactate Threshold Present (n = 7)								
1	12.0	3.3	5.9	1.1	8.5	1.8	9.3	2.3
2	13.5	5.2	9.0	1.6	9.2	1.7	9.9	2.4
3	14.4	4.7	10.8	1.5	10.3	1.6	11.4	2.1
4	19.4	6.1	11.9	1.3	14.2	3.0	14.0	2.6
5	17.0	2.8	11.0	0.9	11.0	0.9	10.6	1.1
6	18.1	4.0	12.0	1.1	13.8	1.5	13.7	1.6
7	16.7	6.0	9.1	1.9	12.2	2.6	12.5	3.4
Mean ± SD	15.9 ± 2.7*	4.6 ± 1.3	10.0 ± 2.2†	1.3 ± 0.4†	11.3 ± 2.2	1.9 ± 0.7	11.6 ± 1.8	2.2 ± 0.7
Lactate Threshold Absent (n = 9)								
8	9.5	5.2	—	—	10.0	4.3	—	—
9	10.3	3.7	—	—	10.0	1.7	9.4	1.7
10	12.6	6.2	—	—	10.9	4.6	—	—
11	9.0	4.4	—	—	9.4	3.6	7.3	2.5
12	10.5	4.9	—	—	10.3	4.0	8.9	3.5
13	13.2	3.0	—	—	—	—	10.9	1.6
14	10.3	3.3	—	—	—	—	9.1	2.6
15	9.9	4.6	—	—	8.1	2.4	—	—
16	9.5	2.6	—	—	8.1	1.7	—	—
Mean ± SD	10.5 ± 1.4	4.2 ± 1.2	—	—	9.5 ± 1.1	3.2 ± 1.2	9.2 ± 1.3	2.4 ± 0.8

*$p < 0.05$ vs patients without lactate threshold; †$p < 0.05$ vs VT-V slope and VT standard.
VO_2 = oxygen uptake; VT Standard = subjective analysis of gas exchange; VT-V slope = computerized analysis of respiratory gas exchange data.

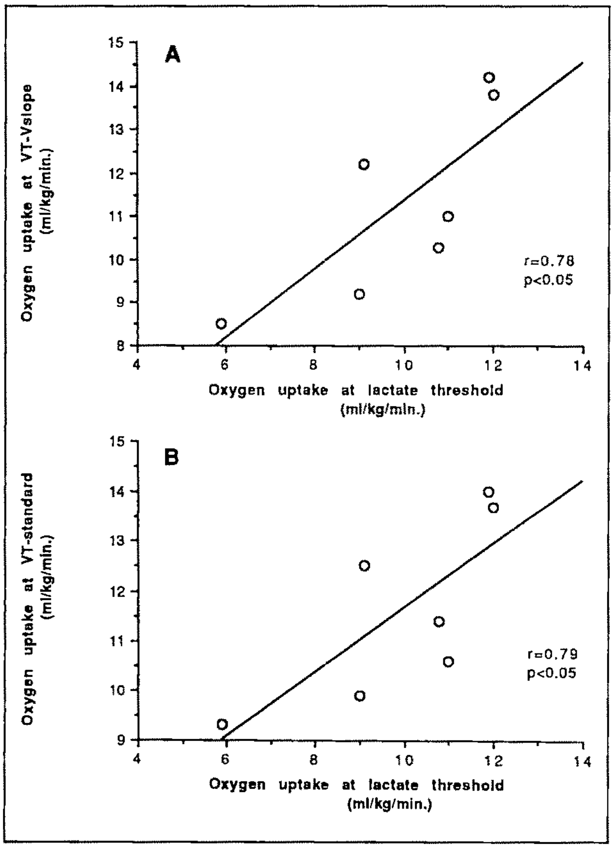

FIGURE 3. Scatter plots of oxygen uptake at anaerobic threshold in 7 patients in whom lactate threshold was detected. Oxygen uptake at lactate threshold significantly correlates with those determined by computerized V-slope method (VT-V slope, *A*) and subjective analysis of respiratory gas exchange (VT-standard, *B*). *Regression lines* are shown.

Rajfer et al[9] also identified subsets of patients with severe aerobic impairment in whom anaerobic threshold could not be detected. The inability to detect lactate threshold in severe CHF is related to the extremely limited work load capacity in these patients. Despite extremely low work loads, patients with severe CHF demonstrated anaerobic metabolism from the onset of exercise.

In patients with mild to moderate CHF in whom lactate threshold was detected, the relation between lactate and ventilatory threshold was similar to that of previous reports. The correlation coefficients of 0.78 and 0.79 for the V-slope and standard methods of determination of ventilatory threshold, respectively, compare favorably with the r value of 0.81 reported by Wilson et al,[6] but are below the r value of 0.96 reported by Matsumura et al.[8] As reported in normal subjects,[12] the ventilatory threshold determined by the V-slope method is closer to the lactate threshold than is ventilatory threshold determined by standard plots.

Whereas arterial lactate concentration increased linearly from the onset of exercise, ventilatory threshold could still be detected in approximately 50% of patients with severe CHF. The point of respiratory compensation, rather than anaerobic threshold, may have been detected in these patients. This explanation is consistent with high relative VO_2 at ventilatory threshold determined in this group. Factors other than blood lactate concentration may have also affected the ventilatory response during exercise. Patients with McArdle's syndrome (a congenital metabolic myopathy in which skeletal muscle lacks the ability to produce lactate) may still manifest criteria for detecting ventilatory threshold determination during graded exercise.[16] Similarly, gly-

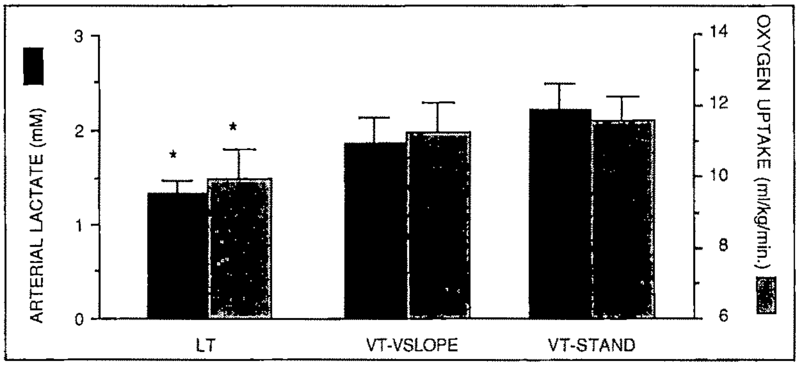

FIGURE 4. Arterial lactate concentration *(black bars)* and oxygen uptake *(stippled bars)* at anaerobic threshold determined by analysis of arterial lactate concentration (LT), computerized analysis of respiratory gas exchange data (VT-VSLOPE), and subjective analysis of gas exchange (VT-STAND). Lactate threshold occurs at significantly lower arterial lactate concentration than those of both VT-V slope and VT standard. *p <0.05.

cogen depletion in normal subjects decreases blood lactate concentration, but increases minute ventilation during exercise.[17] Our findings demonstrate that in patients with severe CHF, criteria for ventilatory threshold were present even in the absence of a detectable lactate threshold.

Clinical implications: An objective measure of functional impairment is needed in patients with severe CHF, because they are most likely to be involved in therapeutic drug trials. A power-assisted bicycle ergometer that provides extremely low work loads may allow detection of anaerobic threshold in severely impaired patients. Submaximal steady-state exercise protocols to assess VO_2 or lactate kinetics may provide an alternative means of assessing functional capacity in patients with severe CHF.[18]

In patients with mild to moderate CHF (peak VO_2 >14 ml/kg/min), the computerized V-slope method is preferable to standard plots, because the values for ventilatory threshold are determined objectively and are closer to the lactate threshold point than are those determined by subjective interpretation of gas exchange data.

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Left Ventricular Dysfunction Due to Atrial Fibrillation in Patients Initially Believed to Have Idiopathic Dilated Cardiomyopathy

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Ten patients aged 22 to 80 years (median 57) with severe left ventricular (LV) dysfunction and atrial fibrillation (AF) with rapid ventricular response were evaluated after therapy. Because most patients were unaware of their arrhythmia, duration was usually unknown. All patients had heart failure symptoms; 9 presented with New York Heart Association class III or IV disability, and 1 with class II disability. Initial LV ejection fraction ranged from 12 to 30% (median 25). No patient had symptomatic coronary artery disease (4 underwent angiography). Myocarditis and infiltrative processes were excluded by biopsy in 5 patients. All patients were considered initially to have idiopathic dilated cardiomyopathy with secondary AF. Ventricular rate was controlled in all patients, with sinus rhythm restored in 5. At follow-up (median 30 months, range 3 to 56), all patients were asymptomatic. LV ejection fraction after treatment ranged from 40 to 64% (median 52). It is concluded that in some patients initially considered to have idiopathic dilated cardiomyopathy, AF with rapid ventricular response may be the primary cause rather than the consequence of severe LV dysfunction. LV dysfunction may be completely reversible with ventricular rate control.

(Am J Cardiol 1992;69:1570–1573)

The clinical entity of reversible left ventricular (LV) dysfunction secondary to chronic tachycardia is now well-documented,[1-7] and in most patients, the underlying arrhythmia was supraventricular tachycardia. The deleterious effects of chronic tachycardia on LV function have been highlighted further by an animal model of congestive heart failure produced by rapid atrial or ventricular pacing.[8-16] Despite reports of "tachycardia-induced cardiomyopathy," atrial fibrillation (AF) in the absence of other heart disease is generally considered a benign entity, although 2 recent case reports suggested the contrary.[17,18] We report on 10 patients who had congestive heart failure, severe global LV hypokinesia and AF with a rapid ventricular response. The admitting diagnosis of all patients was "idiopathic" dilated cardiomyopathy with secondary AF. All 10 patients had marked improvement in LV function and complete resolution of the symptoms of heart failure with ventricular rate control.

METHODS

Ten patients were identified from our clinical practice between 1985 to 1990 with AF and congestive heart failure. A systematic review of all patients with AF and LV dysfunction seen during this time period was not performed. All patients presented with AF, rapid ventricular response, symptoms and physical findings of congestive heart failure, and evidence of LV dysfunction by echocardiography or left ventriculography. Anatomic valvular heart disease was excluded by clinical evaluation and echocardiography. Alcoholic heart disease was excluded by history, and absence of clinical and laboratory evidence of alcohol abuse. Four patients (aged 36 to 61 years) underwent coronary angiography, and 5 underwent endomyocardial biopsy.

Awareness of dysrhythmia and duration of AF were assessed in all patients. New York Heart Association functional class was determined before and after treatment. Medical records were reviewed for type of treatment, initial heart rate, heart rate after treatment, and length of follow-up.

The initial ejection fraction was determined from echocardiographic dimensions in 8 patients by using a modified Quinones method.[19] LV measurements were obtained as an average of ≥ 5 beats during AF and of 3 beats during sinus rhythm. In 2 patients, the initial ejection fraction was obtained by biplane LV angiography, using a Simpson's Rule.[20] All follow-up determinations of ejection fraction were performed using echocardiography.

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TABLE I Clinical Characteristics of 10 Patients with Atrial Fibrillation and Congestive Heart Failure

					Follow-Up				
Pt.	Age (yr) & Sex	Initial NYHA Functional Class	Initial Heart Rate (beats/min)	Initial Ejection Fraction (%)	Heart Rate (beats/min)	Rhythm	Ejection Fraction (%)	Type of Treatment*	Duration (mos.)
1	22F	III	175	25	66	AF	52	Amiodarone (digoxin, enalapril)	30
2	36M	IV	140	29	50	SR	52	DC cardioversion (digoxin, quinidine)	22
3	38M	III	180	12†	50	AF	40	DC cardioversion (digoxin, quinidine, nifedipine)	35
4	53F	III	120	28	70	SR	61	DC cardioversion (digoxin, enalapril)	30
5	55F	IV	150	20	80	SR	54	Amiodarone (digoxin, lisinopril)	56
6	58M	III	150	24	60	AF	52	Digoxin, encainide (diltiazem, captopril, α-methyldopa)	14
7	60F	III	140	28	50	AF	50	Amiodarone (diltiazem)	44
8	60M	IV	130	23†	50	SR	64	DC cardioversion (digoxin, lisinopril, flecainide)	30
9	61M	III	140	25	60	SR	50	Amiodarone (captopril, digoxin)	3
10	80F	II	120	30	70	AF	60	Digoxin, propranolol	21

*Primary treatment that led to ventricular rate control or conversion to sinus rhythm is noted; other cardiac medications (with exception of diuretics) used at time of follow-up are in parentheses.

†Ejection fraction determined by ventriculography, rather than echocardiography.

AF = atrial fibrillation; DC = direct-current; NYHA = New York Heart Association; SR = sinus rhythm.

RESULTS

Clinical characteristics: Clinical characteristics of the 10 patients are listed in Table I. All patients had little or no awareness of palpitations or dysrhythmia, despite initial ventricular rates of 120 to 180 beats/min (median 140); consequently, the duration of AF could not be determined reliably. Most patients sought medical attention only when symptoms of heart failure developed. Nine patients presented with New York Heart Association class III or IV symptoms, and 1 with class II.

The types of treatments used are listed in Table I. Four patients were maintained in normal sinus rhythm, 3 in normal sinus rhythm with intermittent AF, and 3 in AF with a controlled ventricular rate.

Patient 10 had T_3 thyrotoxicosis with secondary AF. With rate control, her LV ejection fraction increased from 30 to 60% at 8-month follow-up, despite continued marked suppression of thyroid-stimulating hormone. Consequently, the LV dysfunction was most likely due to uncontrolled AF rather than to any direct effect of thyroid hormone.

Patients 1 and 6 had poorly controlled hypertension at presentation. Although afterload reduction (angiotensin-converting enzyme inhibitors) may have contributed to improved ventricular function, the magnitude of improvement (>100%) was unlikely the result of afterload reduction alone. Patients 4, 5 and 8 had mild hypertension and received angiotensin-converting enzyme inhibitors. These 3 patients had no echocardiographic evidence of hypertensive heart disease, and marked improvement of LV function was not accompanied by significant change in blood pressure.

Angiographic findings: Results of coronary angiography were normal in 3 patients. One patient had a significant stenosis (80% of the diameter) of the distal circumflex artery, but no angina, evidence of infarction, or regional wall motion abnormalities. He did not receive antianginal treatment. The 6 patients (aged 22 to 80 years) who did not undergo coronary angiography did not have symptoms or risk factors for coronary disease and did not receive treatment for ischemia that could account for the observed improvement.

Endomyocardial biopsy: Endomyocardial biopsy was performed in 5 patients. The results of these biopsies were negative for myocarditis (according to the Dallas criteria[21]) and any infiltrative processes. In the remaining 5 patients, there were no systemic symptoms or clinical findings suggestive of myocarditis or infiltrative processes.

Evaluation of left ventricular function: Ejection fraction before and after treatment, corresponding heart rate, and rhythm are listed in Table I. Initial median LV ejection fraction ranged from 12 to 30% (median 25). With treatment, ejection fraction doubled (range 40 to 64%, median 52). The serial follow-up LV ejection fractions of 3 patients are shown in Figures 1 to 3, because they provide insight into the relation between atrial rhythm, ventricular rate and LV function. An example of the decrease in heart size with treatment is shown in the chest radiographs in Figure 4.

Follow-up: Follow-up ranged from 3 to 56 months (median 30). The 7 patients who remained asymptomatic maintained sinus rhythm or AF with controlled ventricular response. Three patients had recurrent AF with rapid ventricular response; all 3 had recurrent symptoms of heart failure, again without being aware of the dysrhythmia.

DISCUSSION

In the last 40 years, congestive heart failure in association with chronic sustained supraventricular tachycardia was reported in several small series and single case reports.[1-7] These reports suggested that chronic, uncontrolled tachycardia may result in severe global LV dysfunction that may resolve completely over a period of several months with rate control. In some patients, permanent damage could occur.[3] Our initial review of the prior 40 years of literature yielded only 3 reports of AF and reversible heart failure.[17,18,22] However, further review revealed that AF alone was suggested as the cause of dilated cardiomyopathy in previously normal hearts as long ago as 1913.[23] Similar reports were published from 1930 to 1949,[24-27] followed by a 40-year hiatus. In 1949, Phillips and Levine[27] described the first series of patients with AF and reversible heart failure and concluded that "auricular fibrillation *per se* may produce cardiac dilatation and progressive congestive failure . . . a truly reversible type of heart failure."

Several mechanisms of tachycardia-induced LV dysfunction have been proposed, including depletion of high-energy phosphate stores,[8] activation of the sympathetic nervous and renin-angiotensin systems,[9,10] depletion of atrial natriuretic factor,[11] and myocardial isch-

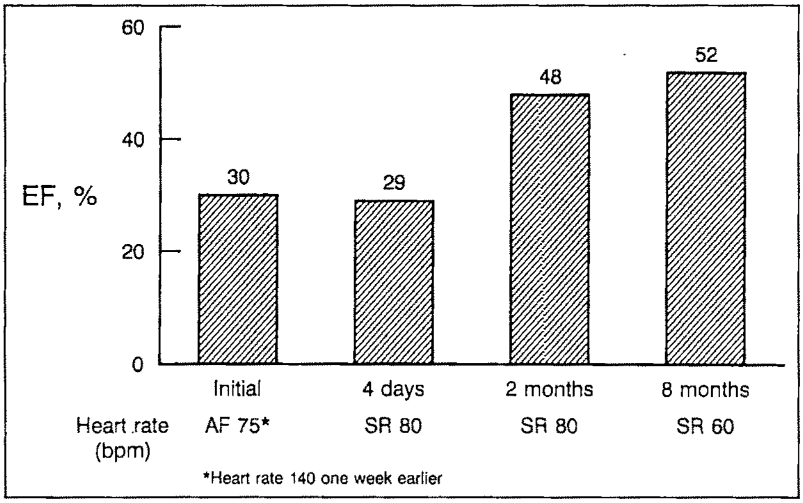

FIGURE 1. Serial ejection fractions (EF) in 36-year-old man who presented 1 week before initial echocardiographic study in atrial fibrillation (AF) with a ventricular response of 140 beats/min. First 2 studies demonstrated essentially identical left ventricular ejection fractions; second was performed after conversion to sinus rhythm (SR). Marked improvement was seen at 2- and 8-month follow-up, despite similar heart rates for all studies.

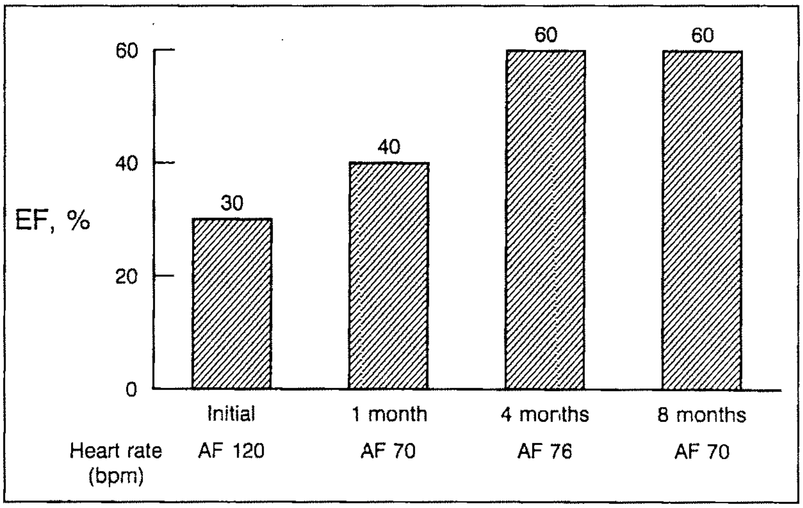

FIGURE 2. Serial ejection fractions (EF) in 80-year-old woman who was in atrial fibrillation (AF) for all echocardiographic studies. Modest improvement was seen after 1 month of rate control, with return to normal ventricular function at 4-month follow-up. Rate control alone resulted in dramatic improvement in ejection fraction without any change in rhythm.

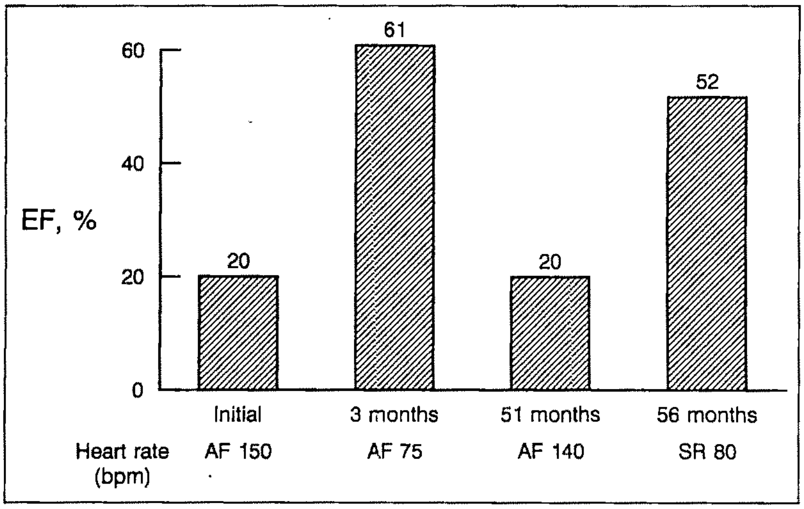

FIGURE 3. Serial ejection fractions (EF) in 55-year-old woman with atrial fibrillation (AF) with rapid ventricular response, EF of 20%, and New York Heart Association class IV heart failure symptoms. With rate control, EF returned to normal. Subsequently (not outlined), sinus rhythm (SR) was restored. Reversion to atrial fibrillation with rapid ventricular response (51 months) resulted in recurrence of symptoms and EF of 20%. With control of arrhythmia, patient again demonstrated marked improvement in ventricular function and resolution of symptoms (New York Heart Association class I).

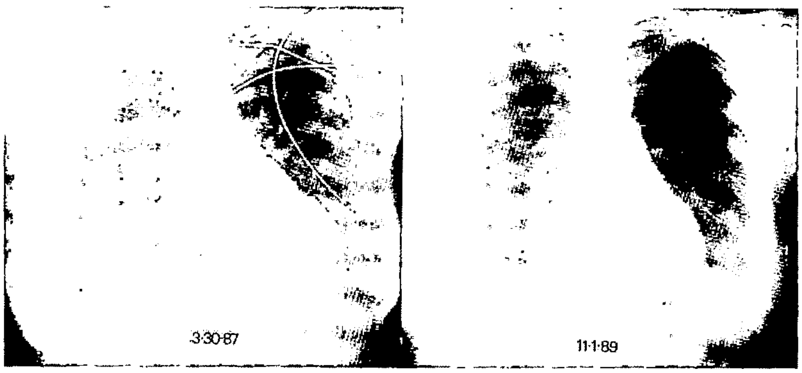

FIGURE 4. Decrease in cardiac size with treatment is demonstrated by chest radiographs of patient 1 (22-year-old woman). Both films were posteroanterior projection. *Left,* atrial fibrillation with ventricular response of 175 beats/min; *right,* atrial fibrillation with controlled ventricular rate of 66 beats/min.

emia with depressed contractility.[12,13] LV hypertrophy, diastolic dysfunction and ventricular remodeling have been described in the experimental animal model.[14-16]

We report the first series of patients with AF and reversible cardiomyopathy since that of Phillips and Levine.[27] All our patients presented with AF and LV dysfunction, and although a normal heart before AF cannot be proved, all echocardiograms after treatment were normal. All patients had little or no awareness of AF. Such patients may be particularly prone to develop LV dysfunction because of prolonged, unrecognized and untreated rapid heart rates. Most patients had only modest improvement immediately after rate control, with gradual improvement occurring during a 1- to 12-month period; this gradual improvement, despite similar heart rates (Figures 1 and 2), argues strongly that the initially decreased ejection fraction measurement was not an artifact of heart rate alone.

Factors other than rate control may have contributed to the improved LV function in our patients. Treatment for hypertension, use of angiotensin-converting enzyme inhibitors, and other therapies for heart failure may have been partially responsible for the improvement in LV function. However, the overall magnitude of improvement in LV function makes it unlikely that these therapies were the major cause of the observed clinical response.

Our conclusions are strikingly similar to those of Phillips and Levine[27] 40 years ago. AF with rapid ventricular response may be a primary cause rather than a secondary effect of severe LV dysfunction. Recognition of this entity has important diagnostic, therapeutic and prognostic implications, because sustained AF is not uncommon, and the associated cardiomyopathy may be completely reversible.

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Myocardial Adenine Nucleotide Concentrations and Myocardial Norepinephrine Content in Patients with Heart Failure Secondary to Idiopathic Dilated or Ischemic Cardiomyopathy

Vera Regitz, MD, and Eckart Fleck, MD

It has been suggested that chronically reduced myocardial adenosine triphosphate (ATP) content causes contractile dysfunction in dilated cardiomyopathy. Because total adenine nucleotides (ATP, adenosine diphosphate and monophosphate) may reflect chronic changes in energy metabolism better than may ATP alone, myocardial ATP, and adenosine diphosphate and monophosphate were determined in endomyocardial biopsy specimens from 19 patients with dilated cardiomyopathy, and decreased left (30 ± 2%) and right (34 ± 3%) ventricular ejection fractions, and from 11 patients with ischemic cardiomyopathy (left ventricular ejection fraction 38 ± 3%), and compared with those from 28 normal control subjects (ejection fraction >55%) to assess myocardial energy metabolism in heart failure. Myocardial norepinephrine was measured simultaneously in the same biopsy specimens to assess if the myocardium studied for adenine nucleotide content was metabolically altered.

Myocardial total adenine nucleotides as well as ATP levels in 19 patients with dilated cardiomyopathy (39 ± 3 and 23 ± 3 nmol/mg of noncollagen protein, respectively) were unchanged in comparison with those of control subjects (37 ± 4 and 23 ± 3, respectively); patients with ischemic cardiomyopathy were not significantly different (30 ± 3 and 19 ± 3, respectively). Myocardial norepinephrine in the same biopsy specimens from patients with dilated (5.8 ± 1.1 pg/μg of noncollagen protein) or ischemic (5.7 ± 1.3) cardiomyopathy was significantly decreased compared with that of normal control subjects (12 ± 1.1).

Normal myocardial total adenine nucleotides and ATP levels together with decreased myocardial norepinephrine in the same biopsy specimens suggest that reduced availability of myocardial adenine nucleotides or ATP is not an early metabolic feature of heart failure nor the cause for the development of contractile dysfunction.

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The triggering event leading to contractile dysfunction in dilated cardiomyopathy remains unknown. It has been postulated that defects in the energy-producing metabolic pathways, and altered concentrations of high-energy phosphates contribute to functional impairment.[1–3] In dilated cardiomyopathy, a linear correlation between functional parameters and myocardial adenosine triphosphate (ATP) content has been proposed,[1,3] and it has been suggested that reduced cytosolic ATP levels may contribute to the development of heart failure.[4] However, recent experiments showed that changes in ATP levels in ischemia over a wide range do not affect systolic function.[5–8]

Final stages of human heart failure due to cardiomyopathy or other heart diseases are characterized by a great number of metabolic defects that are not disease specific and have not been identified as the cause of heart failure. To determine early disease specific metabolic changes, endomyocardial biopsy specimens should be obtained from patients at the early phases of various types of heart failure. In 1 biopsy specimen it is possible to assess adenine nucleotide levels (ATP, and adenosine diphosphate [ADP] and monophosphate [AMP]) and to determine simultaneously myocardial catecholamines (norepinephrine, epinephrine and dopamine). The expected reduction of myocardial catecholamines in heart failure caused by excess sympathetic activity, and decreased reuptake and synthesis provides a marker for altered biochemistry, as well as the efficacy of the biopsy sampling and nucleotide measurements.[9–11]

Between closing of the bioptome in the heart and freezing of endomyocardial biopsy specimens, delays of 10 to 15 seconds are unavoidable. The effect of these delays on adenine nucleotides should be determined to assess if nucleotide levels in endomyocardial biopsy specimens approximate in vivo levels.

The purpose of this study was to determine putative defects in energy metabolism in patients with different stages of heart failure and underlying diseases. Therefore, ATP, ADP and AMP were measured in endomyocardial biopsy specimens from patients with different degrees of impairment of cardiac function, and causes

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TABLE I Hemodynamic Parameters in 19 Patients with Dilated and in 11 with Ischemic Cardiomyopathy, and in 28 Control Subjects

	Cardiomyopathy			
	Dilated (n = 19)	Ischemic (n = 11)	Controls (n = 28)	p Value (dilated/ ischemic)
Left ventricular ejection fraction	30 ± 2*	38 ± 3*	65 ± 2	NS
Left ventricular end-diastolic pressure	16 ± 2	18 ± 4*	11 ± 4	NS
Left ventricular end-diastolic volume index	161 ± 10*	139 ± 16*	94 ± 5	NS
Left ventricular end-systolic volume index	118 ± 10*	87 ± 4*	32 ± 3	†
Mean pulmonary artery pressure	25 ± 2*	21 ± 3*	16 ± 3	NS
Right ventricular ejection fraction	34 ± 3*	40 ± 6*	59 ± 2	NS
Right ventricular end-diastolic volume index	103 ± 8*	74 ± 5	86 ± 2	†
Right ventricular end-systolic volume index	71 ± 8*	46 ± 5	32 ± 2	NS
Mean right atrial pressure	7 ± 1	8 ± 1*	6 ± 2	NS

*Significant ($p < 0.05$) differences in comparison with control subjects; †significant ($p < 0.05$) differences between dilated and ischemic cardiomyopathy.
Data are mean ± SEM.
NS = not significant.

TABLE II Hemodynamic Parameters in Subgroups of Patients with Dilated Cardiomyopathy, Left Ventricular End-Diastolic Pressure > or <20 mm Hg, and Left Ventricular Ejection Fraction < or >30%

	Left Ventricular End-Diastolic Pressure			Left Ventricular Ejection Fraction		
	>20 mm Hg (n = 6)	p Value	<20 mm Hg (n = 13)	<30% (n = 12)	p Value	>30% (n = 7)
Left ventricular ejection fraction	24 ± 2	NS	31 ± 4	22 ± 2	*	40 ± 4
Left ventricular end-diastolic pressure	26 ± 2	*	11 ± 1	18 ± 3	NS	12 ± 2
Left ventricular end-diastolic volume index	206 ± 8	*	149 ± 11	189 ± 10	*	130 ± 12
Left ventricular end-systolic volume index	158 ± 13	*	107 ± 12	148 ± 10	*	78 ± 10
Mean pulmonary artery pressure	36 ± 4	*	18 ± 1	27 ± 3	NS	19 ± 3
Right ventricular ejection fraction	29 ± 3	NS	37 ± 3	29 ± 3	*	42 ± 3
Right ventricular end-diastolic volume index	120 ± 20	NS	93 ± 10	113 ± 12	NS	85 ± 7
Right ventricular end-systolic volume index	88 ± 24	NS	62 ± 10	82 ± 13	*	50 ± 7
Mean right atrial pressure	8 ± 3	NS	5 ± 3	5 ± 2	NS	7 ± 2

*Significant differences ($p < 0.05$) between the 2 groups.
Data are mean ± SEM.
NS = not significant.

of heart failure. To place the expected changes in adenine nucleotides in a framework of developing metabolic changes in heart failure, myocardial catecholamines were measured simultaneously in the same endomyocardial biopsy specimens that were used for adenine nucleotide determination.

METHODS

Patients: Right ventricular endomyocardial biopsy specimens were obtained from 19 patients with dilated cardiomyopathy, and decreased left (30 ± 2%) and right (34 ± 3%) ventricular ejection fractions, and from 11 with ischemic cardiomyopathy (left ventricular ejection fraction 38 ± 3%). Clinical and hemodynamic parameters of all patients are listed in Table I. In patients with dilated cardiomyopathy, myocardial adenine nucleotides as well as norepinephrine were measured in all endomyocardial biopsy specimens. In patients with ischemic cardiomyopathy, myocardial adenine nucleotides were measured in all biopsy specimens, and norepinephrine was measured in 8 of 11. In the cardiomyopathy group, subgroups were formed according to hemodynamic parameters: patients with left ventricular end-diastolic pressure > or <20 mm Hg (n = 6 and 13, respectively), or left ventricular ejection fraction < or >30% (n = 12 and 7, respectively) (Table II).

Furthermore, right ventricular endomyocardial biopsy specimens were available from 28 control patients in whom cardiac disease was suspected, but coronary, valvular, hypertensive or myocardial disease was excluded

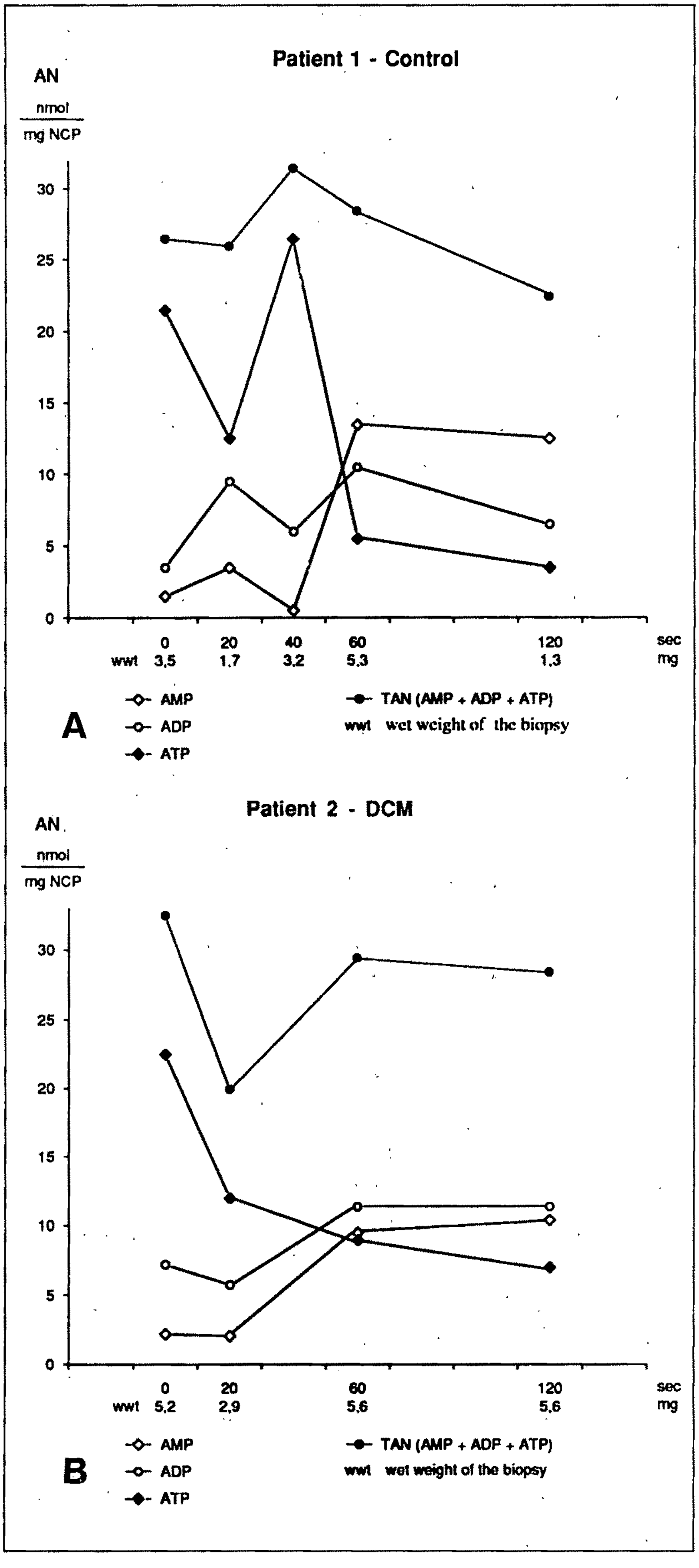

FIGURE 1. Myocardial adenine nucleotide (AN) levels in successive biopsy specimens from patient with left ventricular ejection fraction >55% *(A)*, and patient with dilated cardiomyopathy (DCM) (left ventricular ejection fraction 30%) *(B)*. Total adenine nucleotide (TAN), and adenosine triphosphate (ATP), diphosphate (ADP) and monophosphate (AMP) levels in successive biopsy specimens in which workup was delayed for 0, 20, 40, 60 or 120 seconds are shown. Already after 20 seconds, and even more pronounced after 60 and 120 seconds of ischemia, ATP levels decrease, and AMP and ADP levels increase, whereas total adenine nucleotides remain unchanged. NCP = noncollagen protein.

after complete invasive diagnosis including ventriculography, coronary angiography and histology. In 14 of these patients, myocardial adenine nucleotides were measured, and in the other 14, myocardial catecholamines were measured.

Hemodynamic measurements and angiography: Right and left heart catheterization was performed in all patients (after an overnight fast), using a transfemoral approach (Judkins technique). All medications were withheld on the day of catheterization. Cardiac output was determined by thermodilution technique as the mean of ≥3 measurements. Quantitative biplane ventriculography (30° right and 60° left anterior oblique projections) from the left and right ventricles was performed with a pigtail catheter using 40 ml of nonionic contrast medium (flow 12 ml/s) on a biplane Philips digitized cinesystem. Left and right ventricular volumes and ejection fractions were quantitated according to Simpson's rule[12] (left) and Ferlinz et al[13] (right), using our computerized quantitative analysis system for angiographic data.[14] Normal values for right and left ventricular volumes were previously published.[15] Endomyocardial biopsy specimens were obtained with a 7Fr Cordis (502-300L) bioptome. Three to 5 pieces of tissue were sampled for histologic and biochemical studies and frozen immediately or stored in formaldehyde.

Assessment of adenine nucleotide breakdown after excision of biopsy specimens: Effects of temporal delays on adenine nucleotide breakdown in endomyocardial biopsy specimens were studied in 2 patients. In a control case, 4 endomyocardial biopsy specimens were obtained in 1 catheterization procedure and reserved for the determination of adenine nucleotide breakdown (Figure 1A). In a patient with dilated cardiomyopathy, 5 samples were obtained and reserved for the aforementioned purpose (Figure 1B). The interval between closing the jaws of the bioptome in the heart and freezing biopsy specimens was between 12 and 15 seconds in all 9 samples. Before workup for adenine nucleotide determinations, nonperfused biopsy specimens were kept at room temperature for an additional 0, 20, 40, 60 or 120 seconds.

Biochemical determinations: All biopsy specimens were frozen as quickly as possible (10 to 15 seconds) in dry ice and stored at −70°C until analysis. Samples were homogenized in 4% perchloric acid with 5 mmol of glutathione. After centrifugation, the pellet was used for determination of noncollagen protein,[16,17] and the supernatant was divided for total adenine nucleotides and catecholamine analysis.

Adenine nucleotides were measured in the supernatant using reversed-phase high-pressure liquid chromatography.[18] A Waters solvent delivery system (M510), rheodyne injection unit, C18 column (ODS Hypersil [5 μm]), ultraviolet-detector (Walter M4 81) set at 254 nm, and Waters data station (Maxima 820) were used. All adenine nucleotides were eluted during the first 15 minutes. For quantification, the area under the peaks was compared with that under the standards. The technique was linear in a range from 10 to 2,000 pmol. The sensitivity was 5 pmol/injection. Recovery for amounts of ATP as they were present in endomyocardial biopsy specimens was 95 ± 8% (n = 4). The variability of the high-pressure liquid chromatography procedure was 8% (ATP), 11% (ADP) and 17% (AMP).

Catecholamines were quantitated using electrochemical detection as previously described.[10,11]

Statistical analysis: The Wilcoxon test for unpaired samples was used to compare groups. Data are expressed as mean ± SEM.

RESULTS

Breakdown of adenine nucleotides after excision of biopsy specimens: Myocardial adenine nucleotide concentrations in biopsy specimens in which workup was delayed for of 0, 20, 40, 60 or 120 seconds are shown in Figures 1A (control patient) and B (heart failure patient). ATP decreased after 20 seconds in both patients. At 60 and 120 seconds, ADP and AMP were higher than ATP in both patients, whereas total adenine nucleotides were still unchanged in comparison with the initial values.

Myocardial norepinephrine content in heart failure: In 19 patients with heart failure due to dilated cardiomyopathy, myocardial norepinephrine (in pg/μg of noncollagen protein) was significantly reduced in compari-

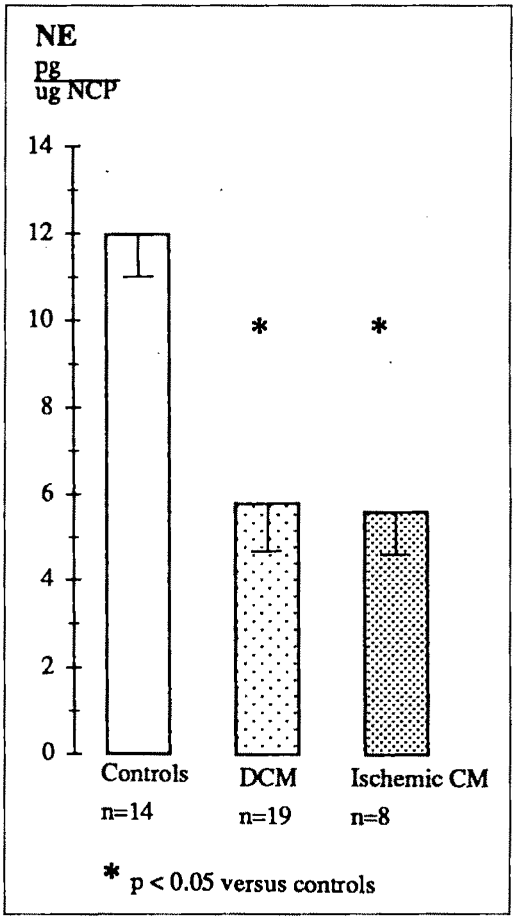

FIGURE 2. Myocardial norepinephrine (NE) in patients with dilated (n = 19) and ischemic (n = 8) cardiomyopathy (CM) is significantly reduced in comparison with that in control subjects (n = 14). Other abbreviations as in Figure 1.

son with control patients (dilated cardiomyopathy 5.8 ± 1.1, and controls 12 ± 1.1). In 8 patients with ischemic cardiomyopathy, myocardial norepinephrine (5.7 ± 1.3 pg/μg of noncollagen protein) was reduced to 47% of that of controls (Figure 2).

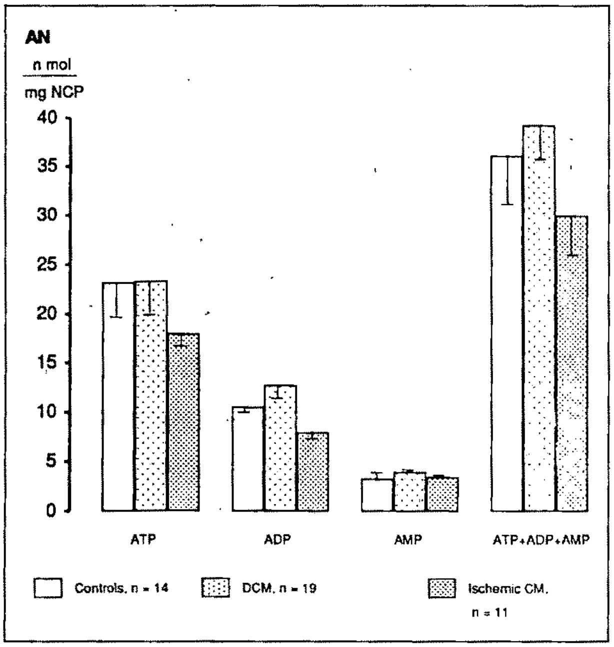

FIGURE 3. Myocardial adenine nucleotides (AN) in patients with dilated (n = 19) and ischemic (n = 11) cardiomyopathy (CM) are not different from those in control subjects (n = 14). ATP, ADP and AMP levels, as well as total adenine nucleotides in 3 patient groups are shown. Other abbreviations as in Figures 1 and 2.

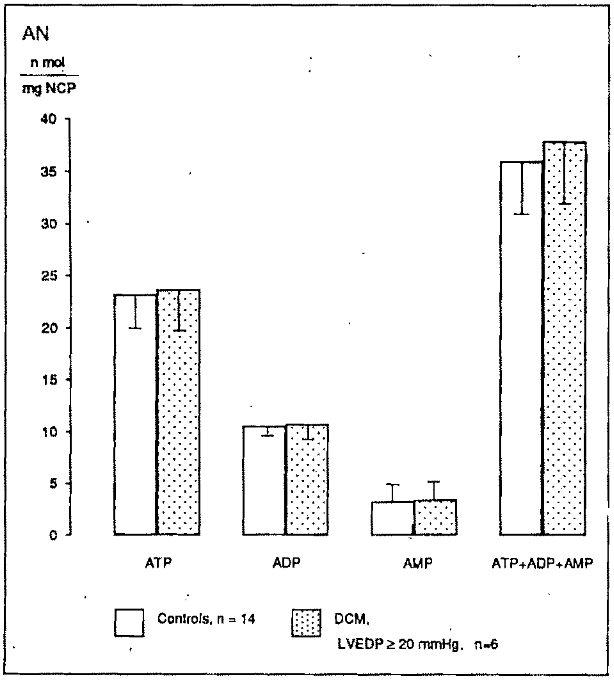

FIGURE 4. Myocardial adenine nucleotides (AN) in patients with dilated cardiomypathy (DCM) and left ventricular end-diastolic pressure (LVEDP) >20 mm Hg show no significant differences from healthy control subjects. ATP, ADP and AMP levels and total adenine nucleotides are presented. Other abbreviations as in Figure 1.

In the 7 patients with dilated cardiomyopathy and left ventricular ejection fraction >30%, myocardial norepinephrine was only slightly reduced (8.7 ± 1.6 pg/μg of noncollagen protein), whereas a severe reduction was found in 12 patients with left ventricular ejection fraction <30% (3.9 ± 1.3; $p < 0.05$).

Myocardial adenine nucleotide content in heart failure: In 19 patients with heart failure due to dilated cardiomyopathy, myocardial total adenine nucleotides (39 ± 3 nmol/mg of noncollagen protein) and myocardial ATP (23 ± 3) were unchanged in comparison with those of control patients (37 ± 4 and 23 ± 3, respectively). This relation was also true for ADP and AMP (Figure 3). In patients with ischemic cardiomyopathy, myocardial ATP concentration and total adenine nucleotides (19 ± 3 and 30 ± 3 nmol/mg of noncollagen protein, respectively; n = 11) were below the nucleotide levels of control patients; however, the differences were not significant (Figure 3).

The subgroups with dilated cardiomyopathy and left ventricular ejection fraction <30% (n = 12; left ventricular ejection fraction 22 ± 2%) also had normal adenine nucleotide concentrations (ATP 26 ± 4 and total adenine nucleotides 43 ± 5 nmol/mg of noncollagen protein). In patients with dilated cardiomyopathy and left ventricular end-diastolic pressures >20 mm Hg, no differences of myocardial ATP (24 ± 4) or total adenine nucleotides (37 ± 5) were observed in comparison with those of control patients (Figure 4).

DISCUSSION

In endomyocardial biopsy specimens from patients with dilated cardiomyopathy and heart failure of different origin, myocardial ATP and total adenine nucleotide concentrations were unchanged in comparison with those of healthy control subjects, whereas myocardial norepinephrine was significantly reduced in the same specimens. This was also true in the subgroups with dilated cardiomyopathy and left ventricular ejection fraction <30% or left ventricular end-diastolic pressure >20 mm Hg.

In the endomyocardial biopsy specimens studied, total adenine nucleotide levels in control patients (37 ± 4 nmol/mg of noncollagen protein) compared well with expected in vivo levels, approximated by measurements in surgically obtained human biopsy specimens (41 ± 5), in animal experiments or in cell cultures.[8,19–21] In contrast, ATP levels in surgical biopsy specimens are higher than those measured by us.[20] Accordingly, our ATP/total adenine nucleotide ratios (0.55 to 0.62) were different from cultured muscle cells where ratios of 0.9 were found in our laboratory (unpublished), with similar values of 0.89 reported in the literature for cultured myocytes.[21] In cell cultures, almost in vivo adenine nucleotide levels may be obtained by the immediate stopping of metabolic processes with perchloric acid. However, when working with human endomyocardial biopsy specimens, short periods of acute ischemia are unavoidable because the time needed for retracting the bioptome, and handling and freezing the tissue is approximately 10 to 15 seconds. This may be the reason for artificially reduced ATP levels. Figure 1 indicates that in endomyocardial biopsy specimens, relatively high ADP and AMP levels are measured even in those that have been frozen and worked up without delay (0 second). If biopsy specimens are kept at room temperature, breakdown of ATP, and increases in ADP and AMP appear to begin during the first 20 seconds, whereas total adenine nucleotides remain stable for a few more seconds, probably due to the well-documented phenomenon that the degradation of AMP is slow in myocytes.[19] Surgically obtained biopsy specimens that can be frozen within approximately 2 seconds (much faster than endomyocardial specimens [10 to 15 seconds]), and where the breakdown of ATP is slowed down by cardioplegia also show reduced ATP/total adenine nucleotide ratios (0.79 to 0.83)[20] in comparison with those of cultured myocytes (0.89).[14] We conclude that due to its fast degradation, the correct determination of ATP in human endomyocardial biopsy specimens is almost impossible. In contrast, total adenine nucleotide content changes less and approximates in vivo levels, at least for approximately the first minute after excision of the biopsy specimen. Because total adenine nucleotides parallel changes in ATP content in metabolic states with chronically decreased ATP levels,[7,22] they probably represent a useful parameter to assess chronic changes in energy metabolism. Thus, unchanged total adenine nucleotides in our patients in comparison with those in control subjects argue against a chronic adenine nucleotide or ATP reduction in early or moderate stages of heart failure and may be even more important than are unchanged ATP levels alone.

There is an ongoing discussion as to whether metabolic parameters in endomyocardial biopsy specimens from the right ventricular septum (where specimens are obtained) mirror the entire heart and may be correlated with left ventricular function. Data from surgically obtained biopsy specimens document that the endomyocardium would be the first place for changes in energy metabolism to be detected if they were present.[20] Recently published results demonstrate a similar behavior of both ventricles for a variety of biochemical changes in heart failure.[23] Detailed studies conducted at the German Heart Institute in explanted hearts showed comparable metabolite levels in the septum, right ventricle and base of the left ventricle.[10,24] In right ventricular endomyocardial biopsies from patients with heart failure, a decrease in myocardial carnitine content, and altered enzyme activities[24,25] suggest that the right ventricular myocardium is metabolically altered.

Functional impairment of the right ventricle is evident in our patients with cardiomyopathy and decreased right ventricular ejection fraction. Reduced myocardial catecholamines in the same endomyocardial biopsy specimens where adenine nucleotides have been measured indicate that the myocardium studied was metabolically affected. In conclusion, normal myocardial adenine nucleotide levels in the presence of a decreased catecholamine content in the same biopsy specimens from patients with impaired cardiac function suggest that a reduction of adenine nucleotides is not an early factor causing contractile impairment in dilated cardiomyopathy.

A relation between decreased myocardial ATP levels and a decrease in ejection fraction (as has been postulated)[1] would be difficult to understand, because the adenosine triphosphatase (ATPase) activity of myosin is saturated at much lower ATP concentrations than are usually available in the cell (half-saturation Michaelis constant: <1 μM; and cellular ATP: approximately 5,000 μM). This low Michaelis constant of the myosin-ATPase explains why myocardial contractility is unaffected in isolated myofibrils, as well as in cardiac myocytes with hyperpermeable plasma membranes, by changes in ATP concentrations between 5,000 and 30 μM.[5,6] There is now accumulated evidence also in intact animals that ATP concentrations, per se, do not determine the maximal ATPase activity of myosin, and consequently, ATP levels are not a direct determinant of contractile function.[7,8]

Study limitations: Earlier methodologic studies showed that the 66% confidence intervals for the determination of adenine nucleotides and norepinephrine in endomyocardial biopsy specimens were approximately 12 and 17% of the mean values of groups of 8 and 14 patients, respectively.[11] Thus, small changes in the range of 15% are probably not detectable by measurements in endomyocardial biopsy specimens.

Normal adenine nucleotide levels in endomyocardial biopsies do not prove that energy metabolism is intact. They only suggest that the supply of ATP meets the demand and that mitochondrial function is probably not a limiting factor. It cannot be excluded that the free energy charge of ATP hydrolysis is decreased, that ATP turnover is decreased or that use of ATP at the contractile element is disturbed.

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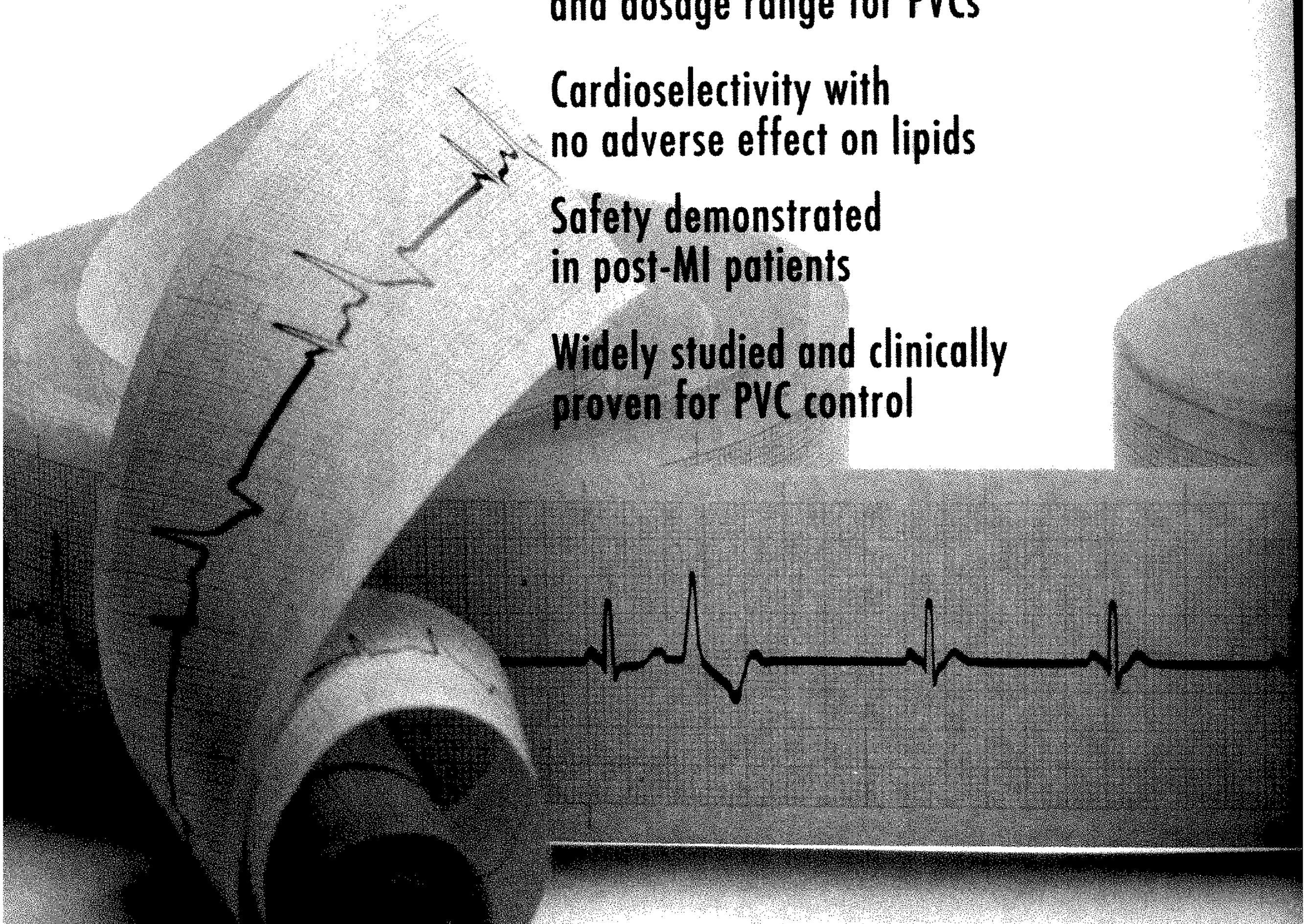

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THE CARDIOSELECTIVE BETA BLOCKER FOR PVC CONTROL

sual starting se	**200 mg b.i.d.**
ptimal /C response	**600 mg to 1200 mg per day**
se in elderly	**Doses above 800 mg per day should be avoided**

ief Summary. See Package Circular for full prescribing information.)

NTRAINDICATIONS: SECTRAL is contraindicated in: 1) persistently severe
dycardia; 2) second- and third-degree heart block; 3) overt cardiac failure;
cardiogenic shock. (See WARNINGS)
RNINGS: Cardiac Failure: Sympathetic stimulation may be essential for support
irculation in patients with diminished myocardial contractility and inhibition by
drenergic receptor blockade may precipitate more severe failure. Although
lockers should be avoided in overt cardiac failure, SECTRAL can be used
tiously when heart failure is controlled with digitalis and/or diuretics. Digitalis and
TRAL impair AV conduction. Withdraw SECTRAL if cardiac failure persists.
Patients Without a History of Cardiac Failure: In patients with aortic or mitral
ve disease or compromised left ventricular function, continued depression of the
ocardium with β-blockers over time may lead to cardiac failure. Digitalize patients at
signs of failure, and/or give a diuretic and observe closely. Withdraw SECTRAL if
diac failure persists.
cerbation of Ischemic Heart Disease Following Abrupt Withdrawal: Abrupt
continuation of some β-blockers in coronary artery disease patients may exacerbate
jina; in some cases, myocardial infarction and death have been reported. Caution
h patients against interruption of therapy without a physician's advice. Even in the
ence of overt ischemic heart disease, withdraw SECTRAL gradually over a period
bout two weeks; observe carefully and advise patients to minimize physical activity
ing this time. (If desired, patients may be transferred directly to comparable doses
n alternative β-blocker without interruption of β-blocking therapy.) If exacerbation of
jina occurs, restart full-dose anti-anginal therapy immediately and hospitalize
ent until stabilized.
ipheral Vascular Disease: β-antagonists reduce cardiac output and can
cipitate/aggravate arterial insufficiency in patients with peripheral or mesenteric
cular disease. Exercise caution and observe such patients closely for progression
rterial obstruction.
**nchospastic Diseases: Patients with Bronchospastic Disease Should, in
eral, Not Receive a β-Blocker.** Because of its relative β_1-selectivity, low doses of
TRAL may be used cautiously in such patients who do not respond to, or cannot
rate, alternative treatment. Since β_1-selectivity is not absolute and is dose-
endent, use lowest possible dose of SECTRAL initially, preferably in divided doses.
ke bronchodilator, e.g., theophylline, or a β_2-stimulant, available in advance with
ructions for use.
sthesia and Major Surgery: The necessity/desirability of withdrawing
ockers prior to major surgery is controversial; the heart's impaired ability to
ond to β-adrenergically mediated reflex stimuli may enhance the risk of excessive
cardial depression during general anesthesia. Difficulty in restarting and
ntaining the heartbeat also has been reported with beta-blockers. If treatment is
tinued, take special care when using anesthetics that depress the myocardium;
lowest possible SECTRAL dose. SECTRAL, like other β-blockers, is a competitive
bitor of β-receptor agonists, so its effects can be reversed by cautious
ninistration of such agents (e.g., dobutamine or isoproterenol). Symptoms of
essive vagal tone (e.g., profound bradycardia, hypotension) may be corrected with
pine.
betes and Hypoglycemia: β-blockers may potentiate insulin-induced
oglycemia and mask some symptoms such as tachycardia; dizziness and
ating are usually not significantly affected. Warn diabetics of possible masked
oglycemia.
rotoxicosis: β-adrenergic blockade may mask some clinical signs (tachycardia)
yperthyroidism. Abrupt withdrawal of SECTRAL may precipitate a thyroid storm in
ents suspected of developing thyrotoxicosis.
CAUTIONS: Impaired Renal or Hepatic Function: While there are no U.S.
lies, foreign published experience shows that acebutolol has been used
cessfully in chronic renal insufficiency. Acebutolol is excreted via the G.I. tract, but
active metabolite, diacetolol, is eliminated mainly by the kidney. A linear
ionship exists between renal clearance of diacetolol and creatinine clearance
); reduce daily dose of acebutolol by 50% when Cl_{cr} is less than 50 mL/min and
5% when it is less than 25 mL/min. Use cautiously in patients with impaired
atic function.
SECTRAL has been used successfully and without problems in elderly patients in
clinical trials without specific dosage adjustment. However, in the elderly, lower
ntenance doses may be required because bioavailability of SECTRAL and its
abolite are approximately doubled.
rmation for Patients: Warn patients, especially those with evidence of coronary
y disease, against interruption or discontinuation of SECTRAL without physician
ervision. Although cardiac failure rarely occurs in properly selected patients,
se patients to consult a physician if signs or symptoms suggestive of impending
, or unexplained respiratory symptoms, develop.
Warn patients of possible severe hypertensive reactions from concomitant use of
renergic stimulants, e.g., nasal decongestants used in OTC cold medicines and
l drops.
ical Laboratory Findings: SECTRAL, like other β-blockers has been associated
development of antinuclear antibodies (ANA). In prospective clinical trials,
ents receiving SECTRAL had a dose-dependent increase in the development of
tive ANA titers. Symptoms related to this laboratory abnormality were infrequent.
ptoms and ANA titers were reversible upon discontinuation of SECTRAL.

Drug Interactions: Catecholamine-depleting drugs may have additive effects when given with β-blockers. Observe patients treated with both agents closely for evidence of marked bradycardia or hypotension which may present as vertigo, syncope/presyncope, or orthostatic changes in blood pressure without compensatory tachycardia. Exaggerated hypertensive responses have been reported from use of β-adrenergic antagonists with α-adrenergic stimulants, including those in OTC cold remedies and vasoconstrictive nasal drops. Nonsteroidal anti-inflammatory drugs may blunt antihypertensive effects of beta-blockers.
Carcinogenesis, Mutagenesis, Impairment of Fertility: Chronic oral toxicity studies in rats and mice, at doses 15 times the maximum recommended (60 kg) human dose, did not indicate carcinogenic potential for SECTRAL. Diacetolol, the major metabolite in man, was without carcinogenic potential in rats at doses up to 1800 mg/kg/d. SECTRAL and diacetolol also had no mutagenic potential in the Ames Test. No significant impact on reproductive performance or fertility was found in rats following SECTRAL or diacetolol doses of up to 240 or 1000 mg/kg/d, respectively.
Pregnancy: *Teratogenic Effects:* Pregnancy Category B: No teratogenic effects were seen in rat or rabbit reproduction studies utilizing SECTRAL doses that were, respectively, approximately 31.5 and 6.8 times the maximum recommended human dose. At this dose in the rabbit, slight fetal growth retardation was noted; this was considered to be a result of maternal toxicity (evidenced by reduced food intake, lowered rate of body weight gain, mortality). Diacetolol studies (doses up to 450 mg/kg/d in rabbits and up to 1800 mg/kg/d in rats) showed no evidence of fetal harm other than a significant elevation in postimplantation loss with 450 mg/kg/d, a level at which food consumption and body weight gain were reduced in rabbit dams; there was a nonstatistically significant increase in incidence of bilateral cataract in rat fetuses from dams treated with 1800 mg/kg/d. There are no adequate and well-controlled trials in pregnant women; SECTRAL should be used during pregnancy only if potential benefit justifies risk to the fetus.
Nonteratogenic Effects: Human studies indicate that acebutolol and diacetolol cross the placenta. Neonates of mothers who received acebutolol during pregnancy have reduced birth weight, decreased blood pressure, and decreased heart rate.
Labor and Delivery: Effect on labor and delivery in pregnant women is unknown. Animal studies have shown no effect of SECTRAL on the usual course of labor and delivery.
Nursing Mothers: Acebutolol and diacetolol appear in breast milk (milk: plasma ratio of 7.1 and 12.2, respectively). Use in nursing mothers is not recommended.
Pediatric Use: Safety and effectiveness in children have not been established.
ADVERSE REACTIONS: SECTRAL is well tolerated in properly selected patients. Most adverse effects have been mild, not required therapy discontinuation, and tended to decrease as treatment duration increases.

The incidence of treatment-related side effects (volunteered and elicited) derived from U.S. controlled clinical trials in patients with hypertension, angina and arrhythmia follows. Numbers represent percentage incidence for SECTRAL (N = 1002) versus placebo (N=314), respectively.

Cardiovascular: Chest pain 2%, 1%. Edema 2%, 1%. *CNS:* Depression 2%,1%; Dizziness 6%, 2%; Fatigue 11%. 4%; Headache 6%, 4%; Insomnia 3%, 1%; Abnormal dreams 2%, 1%. *Dermatologic:* Rash 2%, 1%. *Gastrointestinal:* Constipation 4%, 0%; Diarrhea 4%, 1%; Dyspepsia 4%, 1%; Flatulence 3%, 1%; Nausea 4%, 0%. *Genitourinary:* Micturition (frequency) 3%, <1%. *Musculoskeletal:* Arthralgia 2%, 2%; Myalgia 2%, 0%. *Respiratory:* Cough 1%, 0%; Dyspnea 4%, 2%; Rhinitis 2%, <1%. *Special Senses:* Abnormal Vision 2%, 0%.

The following selected (potentially important) side effects were seen in up to 2% of SECTRAL patients: *Cardiovascular:* hypotension, bradycardia, heart failure. *CNS:* anxiety hyper/hypoesthesia, impotence. *Skin:* pruritus. *Gastrointestinal:* vomitting, abdominal pain. *Genitourinary:* dysuria, nocturia. *Liver and Biliary:* small number of reported cases of liver abnormalities (increased SGOT, SGPT, LDH). In some cases, increased bilirubin or alkaline phosphatase, fever, malaise, dark urine, anorexia, nausea, headache, and/or other symptoms have been reported. In some cases, symptoms and signs were confirmed by rechallenge. Abnormalities were reversible upon drug cessation. *Musculoskeletal:* back and joint pain. *Respiratory:* pharyngitis, wheezing. *Special Senses:* conjunctivitis, dry eye, eye pain. *Autoimmune:* extremely rare reports of systemic lupus erythematosis.

Incidence of drug-related adverse effects (volunteered and solicited) based on SECTRAL dose is shown below. (Data from 266 hypertensive patients treated for 3 months on a constant dose.)

Body System	400 mg/day (N = 132)	800 mg/day (N = 63)	1200 mg/day (N = 71)
Cardiovascular	5%	2%	1%
Gastrointestinal	3%	3%	7%
Musculoskeletal	2%	3%	4%
Central Nervous System	9%	13%	17%
Respiratory	1%	5%	6%
Skin	1%	2%	1%
Special Senses	2%	2%	6%
Genitourinary	2%	3%	1%

Potential Adverse Effects: Certain adverse effects not listed above have been reported with other β-blocking agents and should be considered as potential adverse effects of SECTRAL.
CNS: Reversible mental depression progressing to catatonia, an acute syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuro-psychometrics.
Cardiovascular: Intensification of AV block (see CONTRAINDICATIONS). *Allergic:* Erythematous rash, fever with aching and sore throat, laryngospasm, respiratory distress.
Hematologic: Agranulocytosis, nonthrombocytopenic and thrombocytopenic purpura.
Gastrointestinal: Mesenteric arterial thrombosis, ischemic colitis.
Miscellaneous: Reversible alopecia. Peyronie's disease. The oculomucocutaneous syndrome associated with practolol has not been reported with SECTRAL.
Keep at room temperature, Approximately 25°C (77°F).

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Use of Limb Movement Sensors as Indicators of the Level of Everyday Physical Activity in Chronic Congestive Heart Failure

Simon W. Davies, MRCP, Sally L. Jordan, SRN, and David P. Lipkin, MRCP

The level of everyday physical activity of patients with chronic congestive heart failure (CHF) may be an important reflection of their quality of life. Everyday physical activity is difficult to measure objectively, and may not relate to exercise capacity determined by laboratory exercise testing. A lightweight sensor worn on the wrist or ankle, which provides a cumulative record of limb movement, was evaluated.

The sensor counted reliably when tested in a laboratory rig and during treadmill exercise. In 20 young normal subjects, hourly movement scores showed the expected diurnal rhythm. Twenty-four-hour movement scores in 30 patients with stable CHF were lower than in 20 age-matched control subjects ($p < 0.005$). Movement scores in CHF correlated with a standard questionnaire scale assessing everyday physical activity ($R = +0.72$, $p < 0.001$). Consecutive daily scores varied widely, but wrist and ankle scores were correlated ($R > +0.7$, $p < 0.05$ in each subject), suggesting true day-to-day differences in activity rather than variability in the recording method. Recording for 5 to 6 consecutive days provides a reliable estimate of mean 24-hour movement score for a subject, and mean 24-hour scores were reproducible when subjects were retested after 8 weeks. There was a weak correlation between movement scores and exercise capacity as measured by peak oxygen consumption during maximal treadmill exercise ($R = +0.42$, $p = 0.01$). Quality-of-life score correlated with movement scores ($R = +0.53$, $p < 0.002$) but not with peak oxygen consumption ($R = +0.36$; p = not significant).

Thus, everyday physical activity as assessed by limb movement monitors is reduced in CHF. Level of everyday physical activity may be more relevant to the patient's quality of life than measurement of exercise capacity, and the movement monitors may be valuable to assess functional status and the response to therapies.

(Am J Cardiol 1992;69:1581–1586)

The level of everyday physical activity is important in both health and disease. First, everyday physical activity may reflect the exercise abilities and general well-being of patients with chronic diseases such as heart failure. Second, epidemiologic studies have described relationships between the habitual level of physical activity and the subsequent incidence of coronary heart disease,[1,2] osteoporosis,[3,4] hypertension[5] and mental health.[6] However physical activity is a complex behavior for which there is no convenient and objective measurement.[7,8]

We describe the use of a self-contained device attached to the wrist or to the ankle which cumulatively records limb movement. This device was validated with respect to the number of limb movements directly observed during exercise, and then in daily life with respect to a standard questionnaire for physical activity. We then applied the device to patients with chronic heart failure and to age-matched control subjects, and related the results to a quality-of-life questionnaire and to peak exercise capacity.

METHODS

Device: The movement monitor is a small lightweight rectangular device measuring 36 × 24 × 12 mm, weight 22 g (Dynalog, Medical Scientific Services, Salisbury, United Kingdom) (Figure 1). The transducer is a mercury-in-glass single pole switch, the output from which is sent to a binary counter chain feeding into a count accumulator (the scaling factor set at 16). The power supply is a lithium/manganese dioxide cell, with a life of 5 years.

Counts are displayed by light-emitting diodes giving a 4-digit display. This display is only visible when an external power source (battery pack) is applied; this arrangement has two advantages. First, the patient cannot read the count continuously, and is therefore less likely to try to influence it consciously or unconsciously. Second, the high-power drain usually associated with a continuous light-emitting diode display is avoided, so that a power supply based on replaceable batteries is not necessary. The unit is fully sealed in an acrylic resin case, the only entry points being the display power-up contacts. The case is waterproof and resistant to shatter.

Laboratory validation: The devices were first tested for reliability of counting using a laboratory shaker table (Gallenkamp). Batches of 6 movement monitors were fixed rigidly to the table with the mercury-in-glass switches orientated along the direction of movement. The shaking table was run at 2 to 20 cycles/s for 3 hours on each occasion, and the scores recorded by each device were noted.

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Treadmill exercise validation: Thirty outpatients presenting for treadmill exercise testing for the assessment of coronary artery disease were selected. A device was attached to each ankle, and the counts obtained during the course of the exercise test recorded. The modified Bruce protocol was used, and exercise duration and total distance covered were noted. The total number of steps taken was estimated by recording the number of steps taken over a 30-second period in the middle of each stage, then multiplying by the duration of each stage and summing to find the total.

Young normal subjects: Twenty normal subjects aged 24 to 54 years (median 30) were recruited from the staff of the cardiology department. Monitors were attached to the nondominant wrist and to the ipsilateral ankle, orientated with the long-axis of the mercury-in-glass switch transverse across the long axis of the limb. Subjects were issued a small external battery pack to power-up the display, and were instructed to read the display of both monitors every hour when awake, recording the results on forms provided for the purpose. Subjects were encouraged to wear the devices without interruption, including while bathing, showering or swimming, for periods of 2 to 7 days.

Patients with chronic left heart failure: Thirty patients aged 54 to 81 years (median 67) with chronic left heart failure in New York Heart Association class II and III were recruited from outpatient clinics. Left ventricular ejection fraction determined by radionuclide gated blood pool scanning was $<40\%$ in all patients, and the etiology of heart failure was ischemic heart disease with myocardial infarction occurring at least 1 year previously. Patients were clinically stable for ≥ 3 months before the study: treatment was diuretic drugs in all patients (furesemide 40 to 80 mg/day) and angiotensin-converting enzyme inhibitor in 14 patients (captopril 25 mg twice daily). Exclusion criteria were: (1) a history of recent angina with abnormal ST-segment changes during exertion; (2) significant valvular heart disease on the basis of history, clinical examination, chest x-ray, electrocardiogram and echocardiogram; (3) primary lung disease as judged by history, clinical examination and chest x-ray; each subject was required to achieve $>70\%$ of predicted normal values for lung volumes (forced expiratory volume in the first second, forced vital capacity) and for gas transfer (total lung diffusing capacity for carbon monoxide, lung diffusing capacity for carbon monoxide per liter of accessible lung volume); (4) disturbances of balance or musculoskeletal problems that might limit treadmill exercise.

Subjects performed maximal symptom-limited exercise on a progressive treadmill protocol with respiratory gas measurements. Mixed expired gases were collected and analyzed by mass spectrometer, minute ventilation being determined by argon dilution.[9] Exercise capacity was determined as peak oxygen consumption in units of ml/kg/min.

Devices were attached to the nondominant wrist and ipsilateral ankle, and patients given a small external battery pack to read the device at the same time each day. Patients were advised to continue their normal activities as usual. Daily scores were recorded while the device was worn continuously for a period of between 8 and 14 days. At the end of this period patients completed two questionnaires: the Dallosso questionnaire to assess the level of physical activity,[10] and the Nottingham Health Profile[11] to assess quality of life.

Elderly normal subjects: Twenty healthy control subjects aged 60 to 79 years (median 69) were recruited from the community with the cooperation of a local general practice. These subjects wore the monitors for periods of between 5 and 14 days, completed the questionnaires, and performed a maximal symptom-limited exercise test to determine peak oxygen consumption.

Statistical analysis: Variables are given as median and range, and nonparametric (distribution-free) statistics were used. Unpaired comparisons were obtained using the Mann-Whitney U-statistic and correlations were examined using the Spearman rank coefficient R.

RESULTS

Laboratory rig validation: At shaking rates below 10 cycles/s, recorded counts differed from the actual number of movements by $<1\%$, with $<1\%$ variation between the 6 devices in each test batch. At very high rates of rocking (10 and 20 cycles/s) there was a tendency to

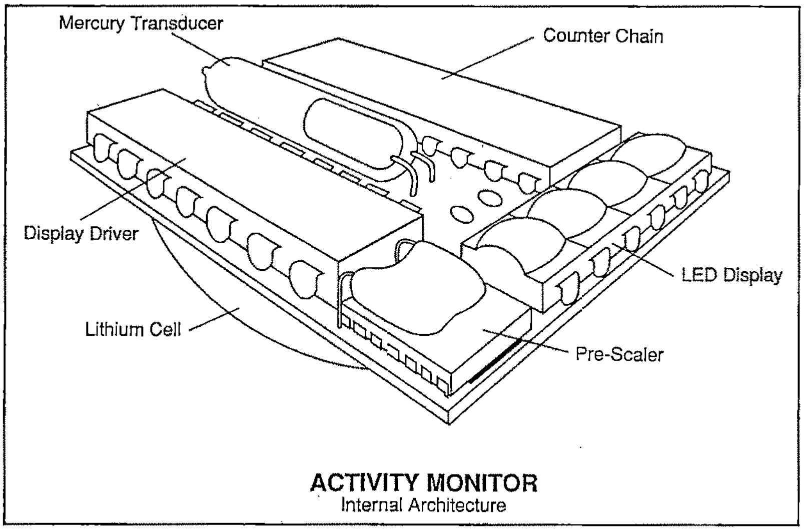

FIGURE 1. Internal construction of the movement monitor device. LED = light-emitting diode.

overcount by 1 to 6%, and there was visible fragmentation of the mercury beads.

Treadmill exercise validation: In 30 patients performing treadmill exercise there was a close correlation between cumulative counts of the device attached to the ankle and the estimated total number of steps taken during the test (R = +0.98, p <0.0001). A tendency to overcount was observed at high work loads. There were weaker correlations between the cumulative counts and exercise duration (R = +0.89, p <0.001), and between the cumulative counts and distance covered (R = +0.89, p <0.001).

Young normal subjects: In the 20 young normal subjects movement scores for consecutive 1-hour periods varied widely (Figure 2). However, for each subject the scores at the wrist and at the ankle for the same 1-hour period were correlated, varying between R = +0.77 (p <0.05) and R = +0.9 (p <0.01). All subjects showed a diurnal pattern in hourly scores, with lower scores during sleep (Figure 2). Cumulative movement scores over each 24-hour period were 869 to 1,957 (median 1,241) at the ankle and 421 to 850 (median 635) at the wrist. The ratio between 24-hour score at the wrist and the ankle in the same subject was 1.6 to 3.6 (median 2.4).

Elderly normal subjects: Twenty-four-hour movement scores were 906 to 2,117 (median 1,193) at the ankle and 369 to 780 (median 580) at the wrist, not significantly different from the young control subjects.

Chronic heart failure: Movement scores for individual 24-hour periods were 56 to 707 (median 267) at the wrist and 245 to 1,760 (median 952) at the ankle. Mean 24-hour score for an individual patient, averaged over the observation period of 6 to 14 days, was 153 to 747 (median 267) at the wrist and 483 to 1,884 (median 952) at the ankle. These scores are significantly lower than the scores of the normal subjects (Figure 3).

The day-to-day variation in scores was large. The coefficient of variation of 24-hour scores from an individual patient was 26 to 101% (median 36) at the wrist, and 18 to 71% (median 32) at the ankle. To achieve an estimate for which the standard error of the mean was ≤15% of the mean would require on average 6 days of recording 24-hour scores for the wrist and 5 days for the ankle. When reproducibility was assessed in 25 patients by repeating monitoring after 8 weeks there were only small changes in mean 24-hour scores at the ankle (median +27, range −102 to +93) and at the wrist (median +37, range −157 to +121).

Twenty-four-hour scores at the wrist and the ankle for individual 24-hour periods were correlated (for each patient R >+0.7, p <0.05). The mean 24-hour scores at wrist and ankle for each patient in the group were correlated (R = +0.81, p <0.0001), and the ratio of ankle to wrist score was 1.6 to 4.1 (median 2.7).

Analysis of the Dallosso questionnaires gave the number of minutes per day spent walking or in other activities requiring >2 kcal/min of energy expenditure, estimated to the nearest 5 minutes. Dallosso scores were 40 to 215 (median 122.5 minutes/day). The Dallosso scores correlated with 24-hour ankle movement scores (R = +0.72, p <0.001) and wrist movement scores (R = +0.60, p <0.001) (Figure 4).

Exercise capacity of the patients with congestive heart failure (CHF), as estimated by peak oxygen consumption, was 7.9 to 25.8 ml/kg/min (median 16.9). Peak oxygen consumption for each patient correlated

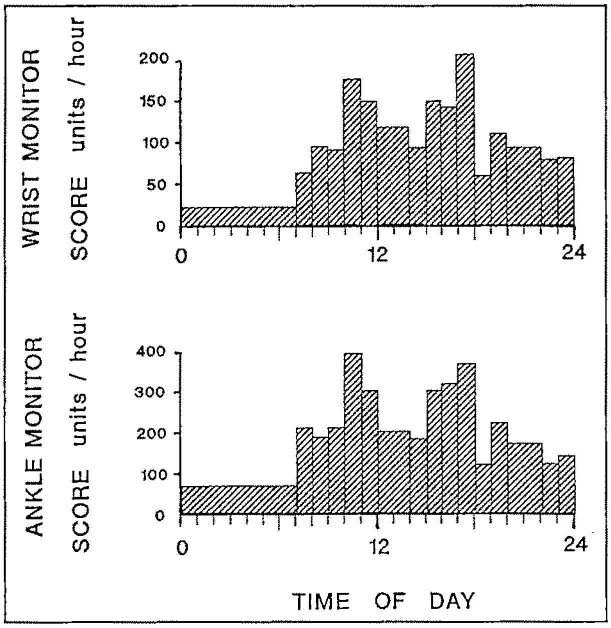

FIGURE 2. Diurnal pattern in movement monitor scores in a normal subject.

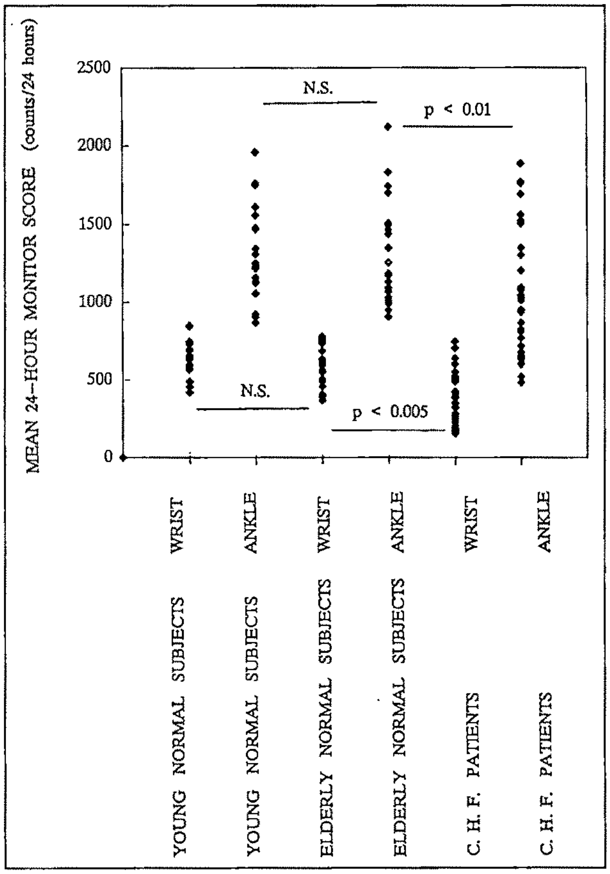

FIGURE 3. Mean 24-hour movement monitor scores in young and elderly normal subjects, and in patients with chronic heart failure. C.H.F. = congestive heart failure; N.S. = not significant.

weakly with mean 24-hour ankle movement score ($R = +0.41$, $p = 0.01$) and with 24-hour wrist score ($R = +0.42$, $p = 0.01$) (Figure 5).

Quality of life as reflected by the overall score of part 1 of the Nottingham Health Profile was 211.6 to 600 (median 532.4), the best possible score being 600 and the worst possible 0. Overall score in the Nottingham Health Profile correlated with ankle ($R = +0.49$, $p = 0.006$) and with wrist ($R = -0.53$, $p < 0.002$) movement scores (Figure 6). Correlations between the Dallosso questionnaire scores for everyday physical activity, exercise capacity (peak oxygen consumption),

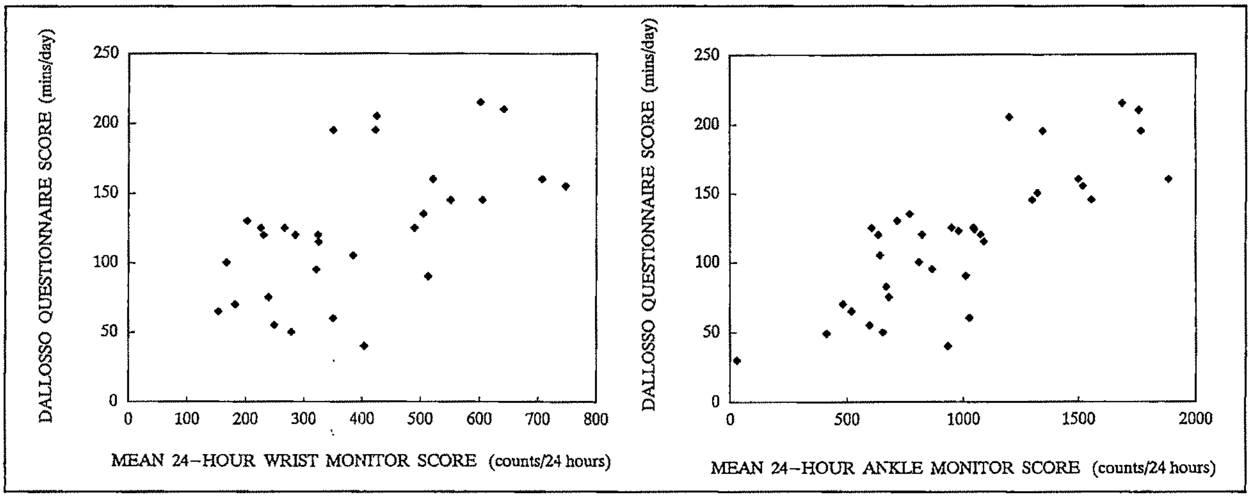

FIGURE 4. Correlation between movement monitor scores and Dallosso questionnaire for everyday physical activity in chronic heart failure.

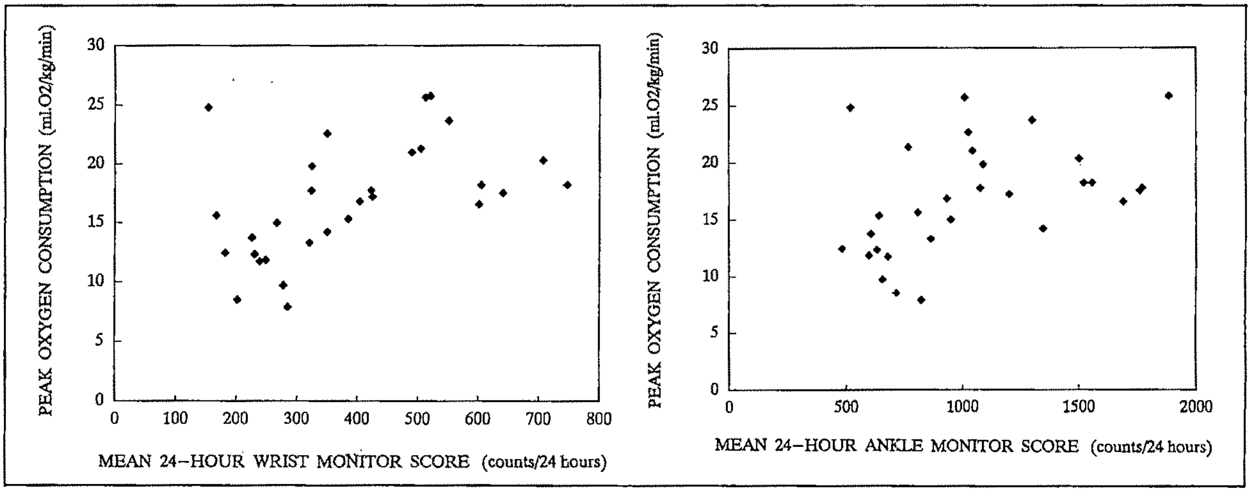

FIGURE 5. Correlation between movement monitor scores and exercise capacity.

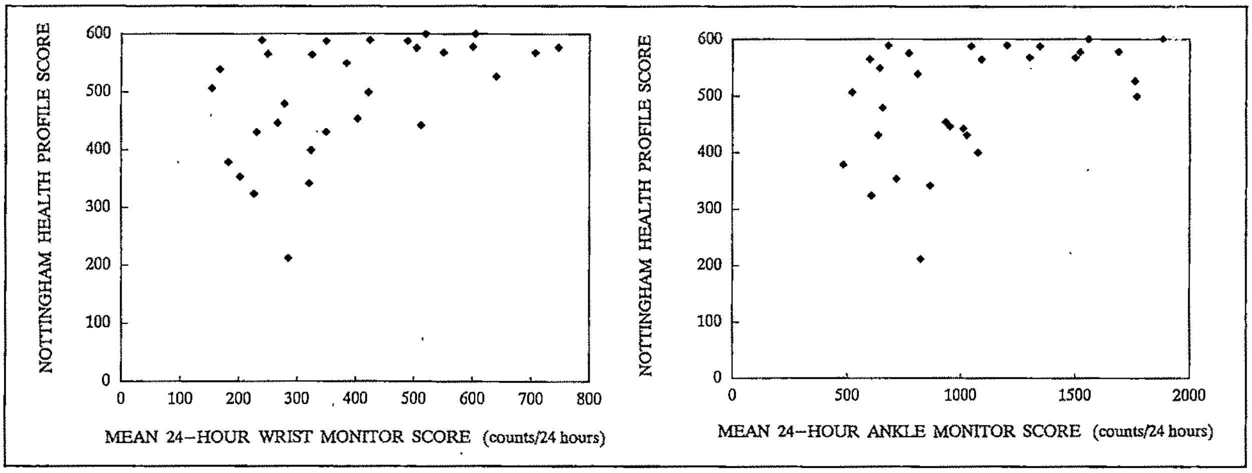

FIGURE 6. Correlation between movement monitor scores and Nottingham Health Profile score for quality of life.

and Nottingham Health Profile score for quality of life are summarized in Figure 7.

DISCUSSION

Methods to assess everyday physical activity: The assessment of everyday physical activity is problematic[7,8] because physical activity is a complex behavior for which there is no agreed standard measurement. Many studies have used questionnaires[1,2] but these are time-consuming, and accurate assessment requires a high level of cooperation by the subject. As an alternative to assessing everyday physical activity, some studies have used measures of exercise capacity such as peak oxygen consumption.[12,13] However it may be questioned whether measurement of peak exercise capacity is relevant to everyday physical activity. Submaximal or endurance tests are more time-consuming but may be more relevant.[14] Ambulatory monitoring of oxygen consumption and of heart rate is possible but has important limitations.[15-19]

Previous studies using movement detectors: Simple pedometers are actuated by impact rather than by the swing of the limb, and are thus difficult to standardize and are only suitable for recording leg movements.[20] Pedometers have been used to compare different modes of cardiac pacing[21] but have not been extensively validated. "Movement monitors" based on mercury switches that respond to tilt are easier to standardize than pedometers and are suitable for arm and trunk as well as leg movements. Movement monitors have been used in several studies[22-25]; the scores correlated with questionnaire assessments of physical activity,[25] and they discriminate between low levels of physical activity[26] for which questionnaires are insensitive. Their suitability for use in patients with CHF has not previously been reported. Limb movements have also been assessed by "accelerometers," which respond to acceleration rather than to tilt.[27,28] In theory they detect the intensity of limb movement[27] but will not be sensitive to slow movements even when these are of large amplitude.[24]

Validation of the movement monitor: The device used in the present study is smaller and lighter than some of the devices previously available.[22] The device was tolerated for periods of up to 14 days by subjects, none of whom reported significant discomfort. It was mechanically robust and waterproof, so that continuous recording of movements was not interrupted during bathing, showering, or heavy occupational exertion. The reliability of the device as a mechanical counter of limb movement was confirmed in the laboratory rig tests and in subjects exercising on a treadmill.

In patients with heart failure, movement monitor scores correlated strongly (magnitude 0.72) with the assessment of everyday physical activity by a previously validated and detailed questionnaire.[10] The correlations previously reported in other groups of subjects range between 0.33 and 0.69.[22,25,29,30] As the principle of operation of these devices is similar, the differences in the strength of these correlations may relate to differences in the pattern or nature of physical activity in these groups of subjects, or to differences in the validity of the questionnaires used.

Observations in normal subjects and in those with chronic heart failure: Use of the device in normal subjects confirmed its acceptability for periods of up to 14 days, and defined a normal range of scores. Detailed analysis of counts each hour revealed the expected difference between hours awake and hours asleep (see Figure 2). Although there are wide variations in the mean 24-hour score between one normal subject and another, and considerable variations between successive 24-hour scores in a given individual, the fact that scores at the wrist and ankles correlate suggest that they reflect true day-to-day differences in physical activity rather than variability inherent in the recording device. The correlation between hour-by-hour scores at the wrist and at the ankle in the young normal subjects ($R > +0.7$ in each subject) also suggests variability in the level of physical activity from hour to hour rather than variability in recording.

Mean 24-hour scores in patients with heart failure were reproducible, and were significantly lower than in age-matched normal subjects, but with a wide range of individual scores. The "active" and "inactive" days in patients with CHF may result from differences in symptom level, as well as day-by-day differences in social demands and intermittent needs to shop, to clean or to garden. This variability reduces the usefulness of movement monitoring to assess the mean level of everyday physical activity of a person or group of subjects. In most persons, it would be necessary to record 5 to 6 consecutive days in order for the standard error of the mean to be $\leq 15\%$ of the mean 24-hour score. Recording for 7 or 8 days might be preferable if there is a weekly pattern to activities. However, the variability itself may be as important as the mean, and in comparing therapies for patients with CHF, both the mean and the single highest 24-hour score might be relevant end points.

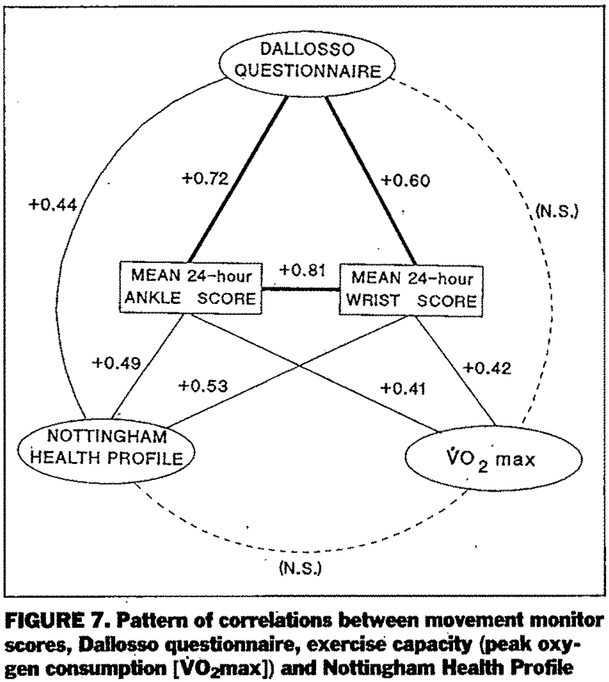

FIGURE 7. Pattern of correlations between movement monitor scores, Dallosso questionnaire, exercise capacity (peak oxygen consumption [$\dot{V}O_2max$]) and Nottingham Health Profile score for quality of life. N.S. = not significant.

Relation to other measures in chronic heart failure: Movement monitor scores correlated with exercise capacity measured as peak oxygen consumption during maximal treadmill exercise. However, the correlations of movement monitor score with peak oxygen consumption and of Dallosso questionnaire score with peak oxygen consumption were both weaker than the correlation between movement monitor and Dallosso scores, suggesting that peak oxygen consumption is a suboptimal measure of everyday physical activity.

The correlation between movement monitor score and the overall "quality of life" score derived from the Nottingham Health Profile suggests that monitor scores relate to the well-being and abilities of the patient. In contrast, the relation between quality of life and peak oxygen consumption was weak, suggesting that peak exercise capacity determined in the laboratory has little relevance to everyday life (Figure 7). Although peak oxygen consumption undoubtedly provides valuable information as to exercise capacity and cardiorespiratory fitness,[12,13] this may vary independently of everyday physical activity and quality of life. A comprehensive evaluation of new therapies in CHF should thus include measures of these different aspects.[18] The pattern of the interrelations between these measures may vary according to the patient group studied; younger patients with CHF may be more active so that limitation by peak oxygen consumption becomes important in everyday life.

Clinical implications: The findings of the present study agree with a clinical impression: patients with CHF perform less everyday physical activity than do normal subjects, but there is wide variation between subjects and also variation from day to day. The lack of correlation of both movement score and quality-of-life score with peak oxygen consumption leads one to question the relevance of laboratory exercise testing to everyday life. Reduced movement score — like reduced exercise capacity — is not specific for heart failure but will also occur in pulmonary, neurologic, rheumatologic, and other disease states.

Leg and arm movement monitors should prove useful in further research since they are well tolerated, durable, and relatively inexpensive. They may be more objective and less demanding of patient cooperation than a detailed questionnaire, and it can be argued that they are more relevant to quality of life than peak oxygen consumption. They may be especially suitable for those unable to exercise on the treadmill, such as the very elderly. They may thus be valuable (1) to assess the response to new therapies in conditions such as chronic left heart failure, and (2) in prospective epidemiologic studies of the influence of everyday physical activity on the subsequent incidence of disease.

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Effect of Quinapril on Blood Pressure and Heart Rate in Congestive Heart Failure

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The effect of quinapril on blood pressure (BP), heart rate (HR) and their variabilities in 12 patients with severe congestive heart failure (New York Heart Association class III and IV) was assessed using ambulatory electrocardiographic and intraarterial monitoring. Mean ± standard deviation daytime BP was 122/75 ± 20/15 mm Hg at baseline and 113/70 ± 13/16 mm Hg after 16 weeks of therapy with quinapril ($p > 0.05$ for systolic and diastolic BP); mean nighttime BP was 114/69 ± 19/14 mm Hg at baseline and 107/69 ± 15/14 mm Hg with quinapril ($p > 0.05$ for systolic and diastolic BP). Mean daytime HR was unchanged but nighttime HR was reduced from 77 ± 11 to 71 ± 10 beats/min, $p = 0.02$. HR variability (difference between the 75th and 25th percentiles of the frequency distribution of RR intervals) increased from 91 ± 34 to 134 ± 47 ms, $p = 0.008$. The variability of successive differences between RR intervals also increased significantly (75th to 25th percentile = 17 ± 4 ms at baseline and 31 ± 26 ms with quinapril, $p = 0.02$). Long-term quinapril caused clinically unimportant decreases in BP in patients with severe congestive heart failure. An increase in vagal activity caused by the reduction in circulating angiotensin II may account for the effect of converting enzyme inhibition on HR and its variability.

(Am J Cardiol 1992;69:1587–1590)

Compared with healthy control subjects, patients with congestive heart failure exhibit reduced diurnal variation in heart rate (HR) and blood pressure (BP), and reduced spontaneous HR variability.[1,2] These features, also seen in autonomic failure,[3] are thought to be a result of autonomic dysfunction. Heart failure is characterized by high levels of sympathetic nervous tone[4] and reduced parasympathetic control.[5] It has been suggested that the reduction in vagal activity is the principal cause of low HR variability in patients with heart failure.[2] In addition to vasodilatation, an important property of angiotensin-converting enzyme inhibitors is their interaction with both sympathetic and parasympathetic nervous systems; they appear to reduce sympathetic tone[6] and increase vagal activity.[7] We have used ambulatory intraarterial and electrocardiographic monitoring to determine the effect of long-term therapy with quinapril on BP and HR and their variabilities in severe heart failure.

METHODS

Patients: Twelve patients (10 men and 2 women, mean age 60 years [range 44 to 69]) with chronic, severe heart failure (New York Heart Association class III and IV) due to coronary artery disease (9 patients) or dilated cardiomyopathy (3 patients) were studied. Mean ejection fraction (gated technetium-99m scanning) was 24% (range 13 to 36). All patients were in sinus rhythm and none had been previously treated with angiotensin-converting enzyme inhibitors. No patient was receiving treatment with any other vasodilator; one patient was taking antiarrhythmic therapy (amiodarone). Concurrent therapy with digoxin (3 patients) and diuretic drugs (mean dose of furosemide 83 mg/day [range 40 to 120]) was unchanged for a minimum of 2 weeks before entry into the study and throughout its duration. For ethical reasons no placebo group or phase was included in this study.

Patients were admitted to the hospital for the study. A brachial artery cannula was inserted percutaneously into the nondominant arm and connected to an Oxford ambulatory BP monitoring system. The system and its recording characteristics have been described before.[8] A 24-hour electrocardiogram monitor (Oxford Medilog) was also worn. Over the following 24 hours, BP and an electrocardiogram were recorded onto standard cassette tapes. Calibration of the BP monitoring system was performed twice during the recording period using a mercury sphygmomanometer. Patients kept a diary of events including meal times and sleep periods. After this initial study period a 5 mg dose of quinapril was given; patients then remained supine for 2 hours during which time the intraarterial BP was recorded continuously.

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TABLE I Systolic Blood Pressure and Its Variability at Baseline and After 16 Weeks of Quinapril Therapy

	Baseline	Quinapril	p Value
Daytime mean systolic BP (mm Hg)	122 ± 20	113 ± 13	0.06
Nighttime mean systolic BP (mm Hg)	114 ± 19	107 ± 15	0.25
Mean day–night difference (mm Hg)	9 ± 10	6 ± 7	0.20
Systolic BP variability (interquartile difference) (mm Hg)	16.8 ± 5.3	17.6 ± 4.1	0.60

Statistical significance obtained using Student's t test for paired observations for blood pressure values and Wilcoxon's signed-rank test for indexes of variability.
BP = blood pressure; interquartile difference = difference between 75th and 25th percentiles of the frequency distributions.

Long-term therapy with quinapril was begun at a dose of 2.5 mg twice daily (taken at 10:00 and 22:00 hours); doses were then doubled at 4 weekly intervals to reach 20 mg twice daily between weeks 12 and 16 in all patients. During week 16 patients were readmitted for a repeat 24-hour BP and HR study.

After visual inspection of the BP trace to identify periods of damping or artifact, computer analysis of the intraarterial record was performed as previously described.[8] In addition to mean hourly values, mean values were obtained for 6-hour periods during the day (12:00 to 18:00) and night (00:00 to 06:00 unless the patient diary indicated a different sleep period). Frequency distribution histograms of systolic and diastolic BP values were generated for each 24-hour study period.

Analysis of the 24-hour electrocardiogram tapes was performed on an Oxford Medilog Excel (software version 2.02) system. Ventricular ectopic beats and arrhythmias were identified by the standard analysis system after manual adjustment of the system to ensure these were correctly identified. In addition to a standard analysis the system stores files of all RR intervals and successive differences between RR intervals (non-sinus beats excluded) on a computer hard disk. To exclude beats unlikely to be of sinus origin, signals due to noise and gaps due to tape dropout, the system rejects intervals <⅔ or >3⁄2 of a running average of RR intervals. The frequency distributions are usually displayed graphically but a small addition to the software allowed mean, standard deviation and quartile values to be calculated and printed.

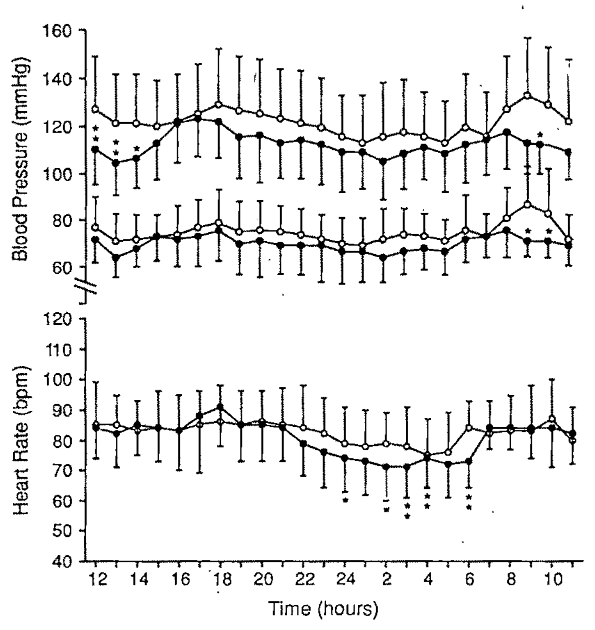

FIGURE 1. Twenty-four-hour blood pressure and heart rate before *(open circles)* and after *(filled circles)* 16 weeks of therapy with quinapril. Results are expressed as mean ± standard deviation. *p <0.05; **p <0.01, paired *t* test.

HR variability is often defined as the standard deviation of the frequency distribution of RR intervals. This value is influenced by intervals at the extreme ends of the frequency distribution necessitating careful editing of the tape to eliminate ectopic beats and artifactual signals. In an attempt to reduce the effect of any artifact we have defined HR variability as the interquartile difference (75th − 25th percentile) of the frequency distribution of the total number of RR intervals for each study. This simple index excludes values at each end of the frequency distribution (as with the triangulation method of Malik et al 1989[9]) and is easily determined by computer analysis. In contrast to RR interval variability, which is affected by exercise and sympathetic tone, the variability of successive differences between RR intervals is believed to be determined almost exclusively by vagal activity.[10] The interquartile difference of the frequency distribution of successive RR differences is therefore an index of vagal tone. Systolic BP variability was defined as the interquartile difference of the frequency distribution of systolic BP values. The computer analysis system did not easily allow calculation of the successive differences between systolic BP values. Diastolic BP variability data are not presented here because they appeared to follow systolic BP variability closely.

Plasma renin and norepinephrine: Plasma renin activity was measured by endogenous substrate assay[11] using samples of venous blood drawn after 40 minutes of bed rest. Plasma norepinephrine was measured by high-performance liquid chromatography.[12]

Statistics: BP and HR were compared using Student's t test for paired data; indexes of variability were compared using the Wilcoxon signed-rank test. A p value <0.05 was considered significant. Values are expressed as mean ± standard deviation.

RESULTS

Blood pressure: No patient had symptomatic hypotension during acute or chronic therapy. After the first dose of quinapril, BP decreased from a mean of 133/78 ± 17/9 to 124/71 ± 16/9 mm Hg 2 hours after dosing (p <0.01 for both systolic and diastolic BP). In contrast to the decrease in BP seen in all patients after acute therapy, 3 patients (2 in New York Heart Association class IV and 1 in class III) experienced an increase in continuously recorded BP during both day and night compared with pretreatment values. The effect of chronic angiotensin-converting enzyme inhibitor therapy on grouped BP and HR profiles is illustrated in Figure 1. The mean decrease in BP with therapy was small and almost equal during both day and night. Mean daytime BP was 122/75 ± 20/15 mm Hg at baseline and

113/70 ± 13/16 mm Hg with quinapril ($p = 0.06$ and 0.16 for systolic and diastolic BP, respectively). Mean nighttime BP was 114/69 ± 19/14 mm Hg at baseline and 107/66 ± 15/14 mm Hg with quinapril ($p = 0.25$ and 0.26 for systolic and diastolic BP, respectively) (Table I). There was no correlation between the percent changes in BP produced by acute dosage and those seen during ambulatory monitoring with chronic therapy ($r = 0.50$, $p = 0.7$). The mean number of hours per patient for which the mean arterial pressure was <80 mm Hg was 4.8 ± 5.4 at baseline and 8.8 ± 7.3 with quinapril ($p = 0.10$). Systolic BP variability did not change significantly with quinapril therapy; the interquartile difference was 16.8 ± 5.3 mm Hg at baseline and 17.6 ± 4.1 mm Hg with quinapril ($p = 0.06$).

Heart rate: Despite the significant decreases in BP after acute administration of quinapril, HR was not changed significantly. Mean HR was 90 ± 13 beats/min at baseline and 87 ± 15 beats/min 2 hours after quinapril ($p = 0.06$). During chronic therapy, daytime HR was unchanged (83 ± 11 beats/min at baseline, 83 ± 9 beats/min during quinapril therapy [$p = 0.99$]); however, there was a significant reduction in nighttime HR from 77 ± 11 to 71 ± 10 beats/min, resulting in an increase in mean day-night difference from 7 ± 3 to 12 ± 8 beats/min (Figure 1, Table II). HR variability increased significantly. The mean interquartile difference of RR intervals increased after quinapril from 91 ± 34 to 134 ± 47 ms, $p < 0.01$. Similarly the interquartile difference of successive differences between RR intervals increased from 17 ± 4 to 31 ± 26 ms after quinapril, $p < 0.05$ (Table II). The effect of quinapril on the variability of BP and HR in a patient with New York Heart Association class IV heart failure is illustrated in Figure 2.

Plasma renin activity and plasma norepinephrine: Mean plasma renin activity was 3.1 ± 2.2 nmol/liter/hour at baseline (upper limit of normal 2.7) and increased to 7.9 ± 6.3 nmol/liter/hour after 16 weeks of quinapril therapy ($p < 0.05$), confirming inhibition of the converting enzyme. Mean plasma norepinephrine was not significantly changed with treatment; levels were 2.57 ± 1.5 nmol/liter at baseline and 2.48 ± 1.6 nmol/liter after 16 weeks of quinapril therapy.

DISCUSSION

This study demonstrated small reductions in BP throughout the day and night with no episodes of potentially hazardous hypotension when patients with severe heart failure were treated with chronic angiotensin-converting enzyme inhibitor therapy. This was in contrast to pronounced decreases in BP after acute treatment. The long-term effects of angiotensin-converting enzyme inhibitor therapy on ambulatory BP in severe heart failure appear to be different from, and cannot be predicted by, their acute hypotensive action. A return toward pretreatment BP during chronic therapy with angiotensin-converting enzyme inhibitors has been noted before, but recordings have been single cuff readings or intraarterial values recorded during the resting phase of invasive hemodynamic studies.[13,14] The reason for the surprisingly small reductions in BP during treatment is not clear. The modest doses of diuretic drugs with which these patients were treated minimize activation of the renin-angiotensin system (as evidenced by only slight elevation of mean plasma renin activity in our patient group) and may have been important in preventing larger reductions in BP during quinapril therapy. Improvements in some indexes of left ventricular function including stroke volume is a feature of angiotensin-converting enzyme inhibitor therapy in heart failure[14-16] and would counterbalance the effect of the reduction in systemic vascular resistance on BP. Like many of the changes in symptoms and hemodynamics seen after angiotensin-converting enzyme inhibitor therapy in heart failure, the increase in stroke volume, particularly dur-

TABLE II Heart Rate and Its Variability at Baseline and After 16 Weeks of Quinapril Therapy

	Baseline	Quinapril	p Value
Daytime mean HR (beats/min)	83 ± 11	83 ± 9	0.99
Nighttime mean HR (beats/min)	77 ± 11	71 ± 10	0.02
Mean day–night difference (beats/min)	7 ± 3	12 ± 8	0.01
RR interval variability (interquartile difference) (ms)	91 ± 34	134 ± 47	0.008
RR interval successive difference variability (interquartile difference) (ms)	17 ± 4	31 ± 26	0.02

Explanations as in Table I.
HR = heart rate.

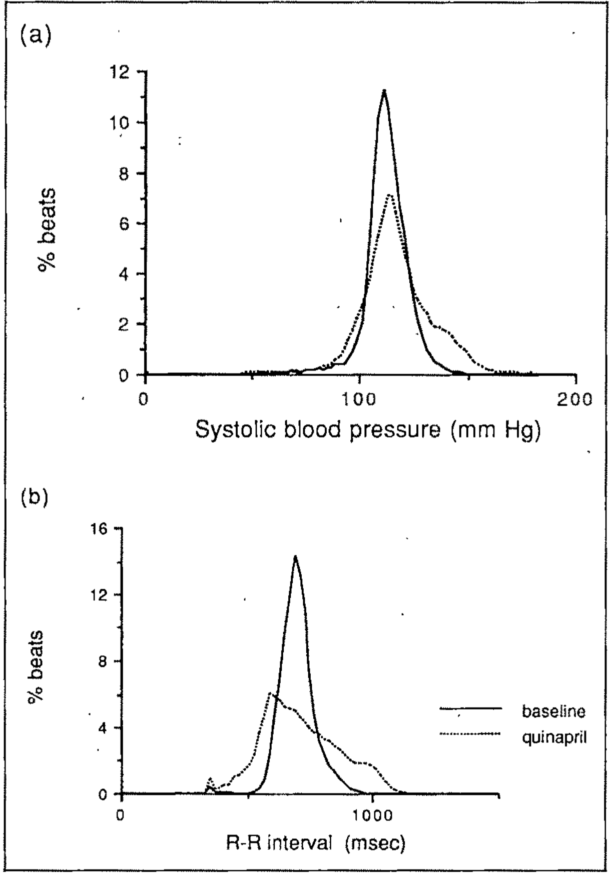

FIGURE 2. Frequency distribution of 24-hour blood pressure *(a)* and heart rate *(b)* before *(solid line)* and during *(broken line)* chronic therapy with quinapril in an individual patient with severe heart failure.

ing exercise, is greater after chronic therapy than after acute treatment.[16]

HR variability increased significantly during quinapril therapy. The major determinant of HR variability is thought to be respiratory sinus arrhythmia, the magnitude of which reflects vagal efferent activity.[17,18] Parasympathetic control is defective in heart failure[5] and this may underlie the low HR variability. The impaired vagal activity may be related to the high levels of circulating angiotensin II; in both animals and humans angiotensin II inhibits the baroreceptor HR reflex[19,20] and has both central and peripheral vagal inhibitory effects.[19,21,22] Angiotensin-converting enzyme inhibitors may increase HR variability in heart failure by increasing vagal tone as a direct effect of reducing circulating angiotensin II. Certainly, baroreflex sensitivity in heart failure is increased by angiotensin-converting enzyme inhibitor therapy.[23] Our data do not exclude the effect of a simultaneous reduction in sympathetic tone, although we were unable to detect any reduction in plasma norepinephrine levels. Angiotensin II exerts stimulatory effects on the sympathetic nervous system,[24,25] and angiotensin-converting enzyme inhibitors appear to have a sympatholytic effect in heart failure.[26,27] However, the influence of the sympathetic nervous system on HR variability is believed to be small compared with that of the vagus.[17]

Low vagal tone evidenced by reduced HR variability is an independent risk factor in patients with coronary artery disease.[28] In addition to their ability to slow the progression of "pump failure" the Veterans Administration Vasodilator Heart Failure Trial II showed that angiotensin-converting enzyme inhibitors also reduce the incidence of sudden death in patients with heart failure.[29] Part of the prognostic benefit of angiotensin-converting enzyme therapy in congestive heart failure may be related to an enhancement of vagal tone reflected in an increase in HR variability.

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Effectiveness of Preload Reserve as a Determinant of Clinical Status in Patients with Left Ventricular Systolic Dysfunction

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The hemodynamic determinants of clinical status in patients with left ventricular (LV) systolic dysfunction have not been established. In the present study, preload reserve — LV distension during exercise — was related to clinical status, and the effect of acute angiotensin-converting enzyme inhibition was examined in 97 patients with ejection fraction ≤0.35 enrolled in the trial, Studies of Left Ventricular Dysfunction (SOLVD). Sixty-one asymptomatic patients (group I) were compared with 36 patients with symptomatic heart failure (group II). Radionuclide LV volumes were measured at rest and during maximal cycle exercise. Group II patients had higher resting heart rates, end-diastolic and end-systolic volumes, and lower ejection fractions (all $p < 0.005$). During exercise, only patients in group I had increased stroke volume (from 35 ± 8 to 39 ± 11 ml/m^2 [mean ± SD; $p < 0.0005$]) due to an increase in end-diastolic volume (from 119 ± 29 to 126 ± 29 ml/m^2 [$p < 0.0005$]), contributing to a greater increase in LV minute output ($p < 0.0001$, group I vs group II). After administration of intravenous enalapril (1.25 mg), LV end-diastolic volume response to exercise was augmented in group II (rest, 140 ± 42; exercise, 148 ± 43 ml/m^2; $p < 0.0005$) and LV output response increased slightly ($p < 0.05$). Thus, in patients with asymptomatic systolic dysfunction, recruitment of preload during exercise is responsible for maintaining a stroke volume contribution to the cardiac output response. In patients with symptomatic heart failure, preload reserve is absent, and the cardiac output response depends solely on heart rate. Enalapril may augment preload reserve.

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Symptoms of heart failure have been linked to an inadequate increase in cardiac output with exercise.[1] During exercise in normal subjects, an increase in left ventricular (LV) stroke volume contributes to augmented cardiac output.[2–5] Stroke volume response may result from recruitment of contractile or preload reserve, or both.[3–6] Functional impairment in patients with heart failure and preserved LV systolic function has been found to result from inadequate preload recruitment.[7] We postulated that in patients with LV systolic dysfunction, preload reserve — LV diastolic distension during exercise — is the critical determinant of stroke volume responsiveness, and therefore influences clinical status. In the absence of contractile reserve, if the left ventricle fails to distend, then stroke volume cannot increase, and augmentation of cardiac output depends solely on heart rate response. Furthermore, we postulated that under such circumstances, drugs that improve functional capacity, may do so in part through restoring preload reserve.

We examined the responses of ventricular volumes during bicycle exercise in 97 patients with LV systolic dysfunction (ejection fraction ≤0.35), and compared them between 61 patients without and 36 patients with symptomatic heart failure. In addition, we sought to determine whether changes in these responses occurred after administration of the angiotensin-converting enzyme inhibitor enalapril.

METHODS

The Studies of Left Ventricular Dysfunction (SOLVD) is a multicenter, randomized, placebo-controlled investigation of the effect of enalapril on survival in patients with LV ejection fraction ≤0.35.[8] These studies involve a treatment trial[9] composed of patients with symptomatic heart failure, and a prevention trial composed of patients without overt heart failure (in whom symptoms are insufficient to warrant treatment). The present report includes 97 patients who entered into a substudy designed to examine the effects of enalapril on radionuclide-derived indexes of ventricular performance. Sixty-one prevention trial patients (group I) and 36 treatment trial patients (group II) were enrolled at New England Medical Center and Vanderbilt University Hospital. This report comprises data derived before randomization. The study was approved by the Human Investigation Review Committees at both centers. All patients gave written informed consent.

Before the study, all patients received oral enalapril, 2.5 mg twice a day for 2 to 7 days to identify side ef-

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TABLE I Patient Characteristics

	Group I (prevention trial; n = 61)	Group II (treatment trial; n = 36)
Age (years; mean ± SD)	58 ± 10	60 ± 10
Men (%)	88	75
Etiology (%)		
Coronary disease	80	83
Dilated cardiomyopathy	20	17
Medications (%)		
Digoxin	10†	53
Diuretics*	7‡	73
Vasodilators* (nonangiotensin-converting enzyme inhibitors)	57§	71

*Withheld prior to study.
†For supraventricular arrhythmias; ‡for hypertension; §for hypertension or ischemic heart disease.

fects, followed by placebo for 14 to 21 days to assess clinical stability and patient adherence. Diuretic drugs were withheld for ≥ 12 hours and vasodilators for ≥ 4 hours before the study. With the patient supine for ≥ 30 minutes before each study, rest and exercise radionuclide ventriculograms were recorded before and after administration of 1.25 mg of intravenous enalapril. After acquisition of the resting scan, serial scans were performed during fatigue-limited maximal supine bicycle exercise, with work load initiated at 30 W, and increased by 15 W every 4 minutes. Scans were acquired during the final 3 minutes of each exercise stage. A scan was repeated at rest and 30 minutes after exercise. Enalapril was then administered, and after a 30-minute delay rest and maximal exercise scans were repeated as previously described. Blood pressure was recorded with a sphygmomanometer at least twice during each scan, with recordings averaged.

For performance of equilibrium-gated radionuclide scans, red blood cells were labeled with approximately 25 mCi of technetium 99-m by a modified in vivo method.[10] Scans were performed in a modified left anterior oblique projection, with caudal angulation.[11–13] Resting and exercise scans were acquired for 8 minutes (minimum 5 million counts) and 3 minutes (minimum 1 million counts), respectively, with each cardiac cycle divided into 32 frames.

Radionuclide studies were analyzed at the SOLVD Radionuclide-Ventricular Performance Core Laboratory at Tufts University, New England Medical Center.[11–13] LV end-diastolic and end-systolic volumes were calculated based on the ratio of background-subtracted LV counts to counts within a 5 ml blood sample corrected for tissue attenuation.[13] LV stroke volume was calculated as end-diastolic volume minus end-systolic volume, LV output as stroke volume times heart rate, and ejection fraction as stroke volume divided by end-diastolic volume. Resting data were compared with those obtained during the final exercise stage in which a complete radionuclide scan was acquired.

Blood samples were drawn for measurement of plasma norepinephrine and renin activity at the 5 time points of radionuclide data analysis during the initial resting scan, at peak exercise, 30 minutes after exercise, 30 minutes after enalapril administration, and at repeat peak exercise. Blood was drawn through an indwelling intravenous line,[14] with the patient supine for ≥ 30 minutes. Plasma samples were shipped on dry ice to the SOLVD Neuroendocrine Core Laboratory at the University of Texas Health Science Center, Houston. Norepinephrine levels were assayed by a radioenzymatic method using the enzyme catechol-*o*-methyl transferase.[15] Plasma renin activity was measured using radioimmunoassay.[16]

Statistical methods: Statistical analyses were performed at the Collaborative Studies Coordinating Center, University of North Carolina. Repeated-measures analyses were used to identify parameters that showed significant difference across the 5 treatment conditions. Once such difference was identified, significant difference between 2 conditions (i.e., rest to exercise or before to after drug administration) was determined by paired *t* test, with adjustment of p values by Bonferroni correction for multiple comparisons. Significant change in exercise response after enalapril was determined by paired *t* test. Comparisons between the 2 patient groups were performed using unpaired *t* test. Results are given as mean ± standard deviation.

RESULTS

Patient characteristics are listed in Table I. Of group II (treatment trial) patients, 7% were in New York Heart Association class I but with previous clinical evidence of heart failure, 66% were in class II, 27% were in class III, and no patient was in class IV.

Mean values of measured parameters at rest and peak exercise, before and after administration of enalapril are listed in Table II. Resting heart rates were higher in group II (treatment trial) than in group I (prevention trial) ($p < 0.005$). At rest, group II patients manifested significantly higher LV end-diastolic ($p < 0.005$) and end-systolic ($p < 0.005$) volumes, and lower ejection fractions ($p < 0.0001$).

Exercise duration was longer in group I than in group II ($p < 0.05$). During exercise, group I patients had a significant increase in end-diastolic volume ($p < 0.0005$), with no change in end-systolic volume, resulting in an increase in ejection fraction ($p < 0.05$) and stroke volume ($p < 0.0005$) (Figure 1). The latter contributed to the increase in LV output ($p < 0.0005$). In contrast, group II had no change in end-diastolic, end-systolic or stroke volume during exercise (Figure 1). In group II, the increase in LV output resulted exclusively from an increase in heart rate, which was of lesser magnitude than in group I ($p < 0.05$). Compared with group II, group I had significantly greater exercise-induced increases in systolic blood pressure ($p < 0.01$), end-diastolic volume ($p < 0.05$), ejection fraction ($p < 0.05$) and stroke volume ($p < 0.001$). Differences in stroke volume and heart rate responses contributed to a greater increase in LV output in group I than in group II ($p < 0.0001$).

Enalapril significantly reduced resting end-systolic volume ($p < 0.01$) and increased ejection fraction ($p < 0.005$) in group II, but not in group I. In group I, enalapril caused no change in LV volumetric response to exercise. In contrast to findings before enalapril ad-

TABLE II Results

	Before Enalapril			After Enalapril	
	Rest	Exercise	Recovery	Rest	Exercise
Group I—Prevention Trial					
Heart rate (min^{-1})	70 ± 13	118 ± 27*	75 ± 14	73 ± 14	119 ± 29*
Systolic BP (mm Hg)	130 ± 19	167 ± 25*	125 ± 18	123 ± 19	163 ± 24*
LVEDV (ml/m^2)	119 ± 29	126 ± 29*	120 ± 31	120 ± 31	125 ± 31*
LVESV (ml/m^2)	85 ± 26	87 ± 26	85 ± 27	84 ± 26	85 ± 27
LVSV (ml/m^2)	35 ± 8	39 ± 11*	35 ± 8	35 ± 8	40 ± 12*
LV output (L/min/m^2)	2.3 ± 0.5	4.4 ± 1.3*	2.5 ± 0.6	2.5 ± 0.6	4.5 ± 1.3*
LVEF	0.29 ± 0.06	0.31 ± 0.08*	0.29 ± 0.06	0.30 ± 0.05	0.32 ± 0.08*
Plasma renin (ng/ml/hour)	1.2 ± 1.7	1.6 ± 2.6	0.9 ± 1.4	2.7 ± 7.5	4.4 ± 10.3
Plasma NE (pg/ml)	346 ± 175	953 ± 718*	369 ± 183	405 ± 310	817 ± 557*
Exercise time (min)		13.1 ± 6.6			12.2 ± 6.4
Group II—Treatment Trial					
Heart rate (min^{-1})	78 ± 14	115 ± 21*	80 ± 15	79 ± 15	115 ± 25*
Systolic BP (mm Hg)	127 ± 23	151 ± 23*	126 ± 22	124 ± 23	147 ± 23*
LVEDV (ml/m^2)	144 ± 46	146 ± 41	143 ± 45	140 ± 42	148 ± 43*‡
LVESV (ml/m^2)	110 ± 42	111 ± 39	109 ± 40	105 ± 37†	112 ± 40*‡
LVSV (ml/m^2)	35 ± 8	34 ± 9	34 ± 9	35 ± 9	36 ± 10
LV output (L/min/m^2)	2.7 ± 0.7	3.8 ± 1.0*	2.7 ± 0.7	2.7 ± 0.7	4.1 ± 1.2*‡
LVEF	0.25 ± 0.05	0.25 ± 0.07	0.24 ± 0.05	0.26 ± 0.06†	0.25 ± 0.07
Plasma renin (ng/ml/hour)	4.2 ± 12.7	5.0 ± 16.4	2.9 ± 8.6	4.7 ± 12.4	6.4 ± 12.6
Plasma NE (pg/ml)	551 ± 273	1,744 ± 1,289*	599 ± 282	624 ± 295	1,422 ± 718*
Exercise time (min)		10.1 ± 6.3			9.2 ± 6.4

*$p < 0.05$ versus rest; † $p < 0.05$ versus before enalapril (recovery); ‡$p < 0.05$ versus before enalapril for change from rest to exercise.
Results are mean ± SD.
BP = blood pressure; EDV = end-diastolic volume; EF = ejection fraction; ESV = end-systolic volume; LV = left ventricular; NE = norepinephrine; SV = stroke volume.

ministration, group II patients after administration of enalapril had significant increases in end-diastolic volume from rest to peak exercise ($p < 0.0005$; $p < 0.05$ vs changes before enalapril) (Figure 1). The magnitude of the exercise-induced end-diastolic volume response after enalapril in group II was similar to that observed in group I (p = not significant for group I vs group II). However, this effect was at least partly offset by an increase in end-systolic volume during exercise, resulting in no significant increase in stroke volume. In group II patients, LV output increased more during exercise after than before enalapril ($p < 0.05$). This effect was related to the fact that before enalapril, stroke volume tended to decrease during exercise, and after enalapril it tended to increase. Exercise duration did not change significantly in either group after enalapril.

Mean plasma renin activity was normal in group I patients, but was abnormally high in group II patients, although this difference was not statistically significant because of the large variation among individual values. The mean plasma norepinephrine level was significantly higher in group II than in group I patients, both at rest ($p < 0.0001$) and at peak exercise ($p < 0.001$), as was the increment in plasma norepinephrine level from rest to exercise ($p < 0.01$). These values did not change significantly after enalapril.

DISCUSSION

During exercise, the normal left ventricle increases stroke volume by a reduction in end-systolic volume, or an increase in end-diastolic volume, or both.[3-5] Reduction or maintenance of end-systolic volume requires sufficient augmentation in the myocardial inotropic state to overcome the exercise-associated increase in afterload. Likewise, the increase in diastolic filling must take place despite reduced filling time. Inotropic and chronotropic responses are both mediated through β-adrenergic stimulation.[17] The diastolic response may also be mediated, at least in part, by β-adrenergic stimulation, resulting in acceleration of diastolic relaxation.[18] Under normal conditions of distensibility, LV end-diastolic volume expands with only modest increment in filling pressure.[2,3]

Previous study of patients with LV systolic dysfunction has indicated that stroke volume response to exercise distinguishes patients with normal functional capacity from those with functional impairment.[19] These differences in stroke volume augmentation have been attributed to variable systolic responsiveness, in part related to the degree of systemic arteriolar dilation.[19] The present findings indicate that symptoms are linked to LV responsiveness during diastole rather than during systole. In our patients with reduced resting LV systolic function, in the absence of overt heart failure (group I), physiologic LV diastolic distension during exercise accounted for augmentation in stroke volume. In the setting of chronic depression of LV systolic function, as after myocardial infarction, ventricular remodeling shifts LV diastolic pressure-volume curve in a manner that yields normal or increased chamber distensibility despite increased diastolic volumes.[20-22] Thus, resting stroke volume and stroke volume response to exercise may be preserved despite loss of contractile function.

In contrast, in our patients with symptomatic heart failure, preload reserve appears to have been exhausted. It is reasonable to presume that these findings are causally related to symptoms of fatigue and exercise intolerance, since they contribute to a lesser cardiac output response to exercise, in association with a shorter exercise duration. The observed absence of preload recruitment in group II represents an abnormality of diastolic performance similar to that which has been identified in patients with heart failure and preserved LV systolic performance.[7]

The explanation for altered LV diastolic response to exercise is open to speculation. Resting LV end-diastolic volumes were larger in symptomatic than in asymptomatic patients. It is possible that the capacity for myocardial remodeling had been exhausted, or that systolic function had failed too rapidly to permit adequate remodeling, resulting in excessive chamber stiffness. Thus, the left ventricle may have been positioned on a relatively steep portion of the diastolic pressure-volume curve, yielding minimal increment in end-diastolic volume for a given exercise-induced increase in filling pressure. In addition, reduced adrenergic sensitivity in patients with heart failure could diminish the normal exercise-induced acceleration of LV diastolic relaxation.[18,23] Lesser chronotropic response in group II, despite greater increments in plasma norepinephrine, indicates reduced adrenergic sensitivity.

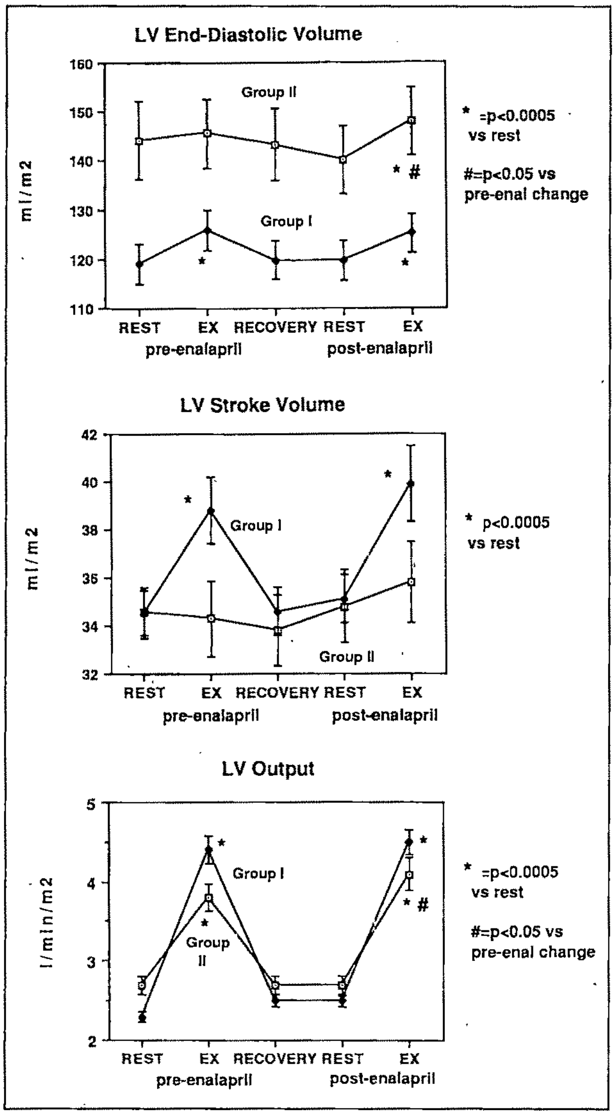

FIGURE 1. Group mean (± SE) values for left ventricular (LV) end-diastolic volume, stroke volume and minute output in group I (prevention trial) and group II (treatment trial) patients. Before enalapril (enal) administration, LV end-diastolic volume and stroke volume increased with exercise (EX) in group I but not group II patients, contributing to a larger LV output response in group I. After enalapril administration, exercise responses in group II patients more closely resembled those observed in group I patients, with an increase in end-diastolic volume and less difference in LV output response between the 2 groups.

Right ventricular dilation and ventricular interaction represent an alternate explanation for the observed difference in LV distension during exercise. In patients with right heart failure, the LV diastolic pressure-volume curve may be displaced upward,[24,25] and this shift may limit an increase in LV filling during exercise.

The effect of angiotensin-converting enzyme inhibitors on cardiac performance has been presumed to result from arteriolar dilation, with reduction in LV afterload and improved stroke volume. Such effects would be analogous to observed nitrate-induced increase in stroke volume during exercise, which has been attributed to afterload reduction.[26] In group II patients, in whom plasma renin levels were elevated, enalapril reduced resting LV end-systolic volume. However, during exercise mean end-systolic volume returned to the values before enalapril, tending to offset augmentation of preload reserve. In contrast, end-diastolic volume response to exercise increased with enalapril, resembling that observed in group I.

Several possible explanations exist for the increase in exercise-induced LV distension with enalapril. First, resting end-diastolic volume decreased after enalapril, presumably toward a shallower segment of its diastolic pressure-volume curve, thus increasing the capacity for preload recruitment. Second, angiotensin-converting enzyme inhibition has been shown to downwardly displace the diastolic LV pressure-volume relation,[27] an effect that may result from withdrawal of angiotensin-induced myocardial diastolic dysfunction[28] or from reduction in right ventricular constraint on LV filling.[13]

Study limitations: We cannot be certain whether group I patients would have manifested comparable increases in LV end-diastolic volume and stroke volume if they had exercised upright. In normal subjects, LV distension has been found to contribute comparably to stroke volume response during supine and upright cycle exercise.[5] Thus, preservation of this response in group I and its absence in group II are likely to be physiologically relevant.

The increase in the exercise-induced response of LV output after enalapril administration in group II patients did not translate into greater exercise duration. The slight improvement in LV output response may have been offset by greater muscular fatigue during the second exercise test. Prior investigations with angiotensin-converting enzyme inhibitors have similarly failed to document early increases in exercise time.[29] Therefore, caution must be exercised in linking our findings to mechanisms for long-term effect on exercise capacity. With chronic angiotensin-converting enzyme inhibition, LV distension during exercise may exceed the observed exercise-induced increase in end-systolic volume, and stroke volume response may increase.

Because we measured LV minute output, rather than forward cardiac output, mitral regurgitation may have influenced our findings. Functional mitral regurgitation may account for the trend toward greater resting LV output in group II versus group I patients. However, it is unlikely that a greater degree of functional mitral regurgitation contributed to the greater stroke volume and LV output response to exercise in group I patients, who were less symptomatic, with smaller ventricular volumes, lesser neurohormonal activation, and longer exercise durations than in group II. Rather, greater functional mitral regurgitation during exercise in group II may have masked differences between the 2 groups. Furthermore, enalapril-induced reduction in functional mitral regurgitation in group II would imply that observed changes in stroke volume and LV output translates into greater increases in forward stroke volume and cardiac output, as has previously been observed during administration of nitroprusside.[30]

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Endothelial Function in Chronic Congestive Heart Failure

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There is evidence that the endothelium plays an important role in the control of human vascular tone by releasing endothelium-derived nitric oxide. The hypothesis that an impairment of this mechanism is involved in the increased peripheral vasoconstriction of patients with chronic congestive heart failure (CHF) was tested. Acetylcholine and N-monomethyl-L-arginine (L-NMMA), a specific inhibitor of nitric oxide synthesis from L-arginine, were infused in the brachial artery of healthy volunteer subjects (controls) and patients with severe CHF. The radial artery diameter was determined by a high-precision A-mode ultrasound device, using a 10 MHz probe. Forearm blood flow was calculated from vessel diameter and blood flow velocity measured simultaneously by Doppler. The blood flow response to acetylcholine was blunted in patients with CHF compared with that in control subjects. In contrast, the decrease in blood flow induced by L-NMMA was exaggerated in CHF, and the blood flow response to nitroglycerin was preserved. The changes in radial artery diameter induced by acetylcholine and L-NMMA were not significant in control subjects and CHF patients, but dilation of the radial artery by nitroglycerin was significantly reduced in CHF. The results demonstrate an impaired endothelium-dependent dilation of forearm resistance vessels in CHF, suggesting a reduced release of nitric oxide on stimulation. In contrast, the basal release of nitric oxide from endothelium of forearm resistance vessels is preserved or may even be enhanced, and may play an important compensatory role in chronic CHF by antagonizing neurohumoral vasoconstrictor forces in CHF.

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Systemic vasoconstriction is a hallmark of advanced chronic congestive heart failure (CHF) and appears to be due to several compensatory mechanisms such as neural, hormonal and local vascular factors.[1] Whereas the neurohumoral factors involved in this impaired vasodilation were studied extensively in the past, the impact of local factors regulating peripheral vasomotor tone and tissue perfusion in CHF are poorly defined. Experimental data suggest that CHF impairs endothelial-dependent dilation of femoral arteries and hind-limb resistance vessels in response to acetylcholine.[2,3] Thus, depression of endothelium-dependent vasodilation may represent 1 local mechanism involved in the impaired metabolic vasodilation in patients with CHF.

The release of endothelium-derived relaxing factor in humans is stimulated by acetylcholine.[4] Basal release of nitric oxide that accounts for the biologic activity of endothelium-derived relaxing factor[5] has been shown to contribute to the control of regional blood flow in humans[6] by using N-monomethyl-L-arginine (L-NMMA), a selective inhibitor of nitric oxide from L-arginine.[7] In the absence of marked vasoconstriction of conduit vessels, changes in blood flow indicate the response of resistance vessels. However, both acetylcholine and L-NMMA have been shown to markedly constrict diseased human conduit arteries, thereby limiting blood flow.[8-10] Therefore, the differential effects of these agents on conduit versus resistance vessels in patients with endothelial dysfunction cannot be assessed by simply measuring blood flow. To identify the endothelium-dependent vasomotor response of large forearm conduit versus small resistance vessels we used a novel ultrasound device to accurately determine forearm arterial diameter, measuring blood flow velocity simultaneously in this vessel. By this approach, the effects of intraarterial infusion of acetylcholine, L-NMMA and nitroglycerin on forearm conduit and resistance vessels were examined in patients with chronic CHF and in age-matched healthy volunteers.

METHODS

Subjects: The control group in this study included 9 normal subjects (3 men and 6 women, aged 30 to 63 years). Subjects with systemic hypertension, diabetes mellitus, hypercholesterolemia, and hematologic, renal and hepatic dysfunction were excluded by a careful history, physical examination, electrocardiogram and laboratory analysis. Nine patients with chronic CHF in New York Heart Association functional class III (Table I) with clinical, radiologic and echocardiographic signs of cardiomegaly and CHF despite treatment with digi-

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TABLE I Characteristics of the Study Cohort

	Normal	CHF
Sex (men/women)	3/6	7/2
Age	52 ± 4	58 ± 4
LV ejection fraction (%)	—	30 ± 3
Peak oxygen consumption (ml/min/kg)	—	15 ± 1
Hemoglobin (g/dl)	14 ± 0.4	15 ± 0.5
Serum sodium (mmol/L)	140 ± 0.9	141 ± 0.7
Resting heart rate (beats/min)	71 ± 6	81 ± 6
Body height (cm)	168 ± 3	169 ± 2
Body weight (kg)	68 ± 4	66 ± 3
Resting forearm blood flow (ml/min)	30 ± 6	27 ± 5
Resting forearm vascular resistance (mm Hg/ml/min)	5 ± 1	6 ± 3
Mean blood pressure	96 ± 4	88 ± 3

CHF = congestive heart failure; LV = left ventricular.

talis, converting enzyme inhibitors and diuretics were studied. In 3 patients, the etiology of CHF was coronary artery disease, and in 5 it was idiopathic dilated cardiomyopathy. One patient had severe left ventricular dysfunction and cardiomegaly after mitral valve replacement, but normal coronary arteries. No patient had history or clinical evidence of hypertension, diabetes, claudication or peripheral arterial occlusive disease. Increased serum and low-density lipoprotein cholesterol levels were found in 3 patients, whereas these levels were within normal range (low-density lipoprotein cholesterol <140 mg/dl) in the remaining 6. No control subject was receiving medication. Patients with CHF were treated with diuretics, converting enzyme inhibitors and digoxin (n = 7), but none received other vasoactive therapy. Digoxin and captopril were stopped 24 hours (48 hours for enalapril) and diuretics ≥12 hours before beginning measurements. Alcohol, caffeine and cigarettes were all prohibited within 8 hours of the study. Written informed consent was obtained from all subjects, and the protocol was approved by the ethical committee of the University of Freiburg.

Determination of arterial diameter: To measure the diameter of conduit arteries we used a recently developed high-resolution A-mode ultrasonic echo-tracking device (Asulab, Neuchatel, Switzerland) that allows measurements of the arterial diameter with a resolution of $\pm 2.5\ \mu m$.[11,12] Recordings of the arterial diameter (8 cm proximal to wrist) were obtained with a focalized 10 MHz transducer positioned perpendicularly to the vessel by Doppler guidance without direct skin contact, using ultrasonic gel as a transmitting medium.[12]

Determination of blood flow velocity: Forearm blood flow velocity was measured by Duplex sonography imaging (5 MHz Doppler and 7.5 MHz 2-dimensional probe, ATL, Ultramark 8) just distal to the 10 MHz device that was used for diameter measurements. After adjusting the Doppler sample to the width of the vessel, mean blood flow velocity was determined by means of standard software of the Duplex scanner after angle correction for the Doppler ultrasonic beam. Arterial blood flow (ml/min) at mid-forearm level was calculated as the product of blood flow velocity and arterial cross-sectional area, obtained from the arterial diameter (measured simultaneously at the time of flow velocity recording) assuming a circular vessel area. Forearm vascular resistance was calculated from arterial pressure (determined invasively; see later) and blood flow. Blood flow velocity was obtained as a mean of 5 consecutive beats (15 beats in 2 patients with atrial fibrillation). Baseline values were calculated from 2 sets of measurements.

Experimental protocol: After insertion of a polyethylene catheter in a brachial artery, blood flow velocity was recorded continuously until stable baseline conditions were obtained (approximately 30 minutes), and arterial blood pressure was measured at baseline and at the end of each drug infusion. Increasing dosages of acetylcholine (10^{-8}, 10^{-7} and 5×10^{-6} M/min) (Dispersa Company, Germering, Germany) were infused in the brachial artery at a rate of 1.7 ml/min, lasting 5 minutes for each concentration. After a second control period to reestablish basal conditions, L-NMMA (Calbiochem, Lucerne, Switzerland) was infused in 6 subjects of both groups over 5 minutes at a dose of 12 nmol/min (infusion rate 1.7 ml/min). The solution was passed through a FlowPore D26 bacterial filter immediately before use. The selection of this dose was based on the report of Vallance et al[6] and on our observations in 5 normal subjects and 3 patients with CHF. Because 4 nmol/min (as used by Vallance et al)[6] did not consistently attenuate the arteriolar dilator response to acetylcholine in our preliminary studies, a threefold higher dose was used. This reduced the blood flow response to acetylcholine by 42 ± 6% compared with that at control, which was consistent with the findings of Vallance et al.[6] To distinguish abnormalities in endothelial function from those of vascular smooth muscle, all subjects received a final intraarterial infusion of nitroglycerin at 5 nmol/min over 5 minutes (rate 1.7 ml/min). Blood flow and diameter data reported for acetylcholine, L-NMMA and nitroglycerin represent the measurements during the last minute of infusion. Radial artery blood flow depends on the variable blood flow distribution pattern of the radial artery. Thus, the relative changes by different interventions should be emphasized, rather than the comparison of absolute values.

Statistical analysis: All data are expressed as mean ± SEM. Statistical comparisons of vessel diameter and blood flow before and during administration of drugs were obtained by analysis of variance for repeated measures, followed by the Student-Newman Keuls test. The statistical significance of differences between groups was determined by Student's *t* test. A p value <0.05 was considered statistically significant.

RESULTS

Patient characteristics: Baseline characteristics of control subjects and patients with CHF were similar for all variables (Table I). Vascular responses to the various interventions did not differ between women and men.

Blood flow response to acetylcholine: Mean blood pressure and heart rate at baseline (before administration of drugs) did not differ between the 2 groups (Table I). The incremental intraarterial infusion of acetylcholine caused no significant changes in systemic blood pressure or heart rate in either group. Forearm blood flow response to acetylcholine in control subjects and CHF patients is illustrated in Figure 1, demonstrating a blunted arteriolar dilator response in patients compared with that in controls. Similarly, forearm vascular resistance did not change with acetylcholine in CHF patients, but decreased in control subjects (Figures 1 and 2). The acetylcholine-induced change in forearm blood flow was not related to baseline vascular resistance.

Blood flow response to nitroglycerin: To determine whether CHF affects smooth muscle reactivity directly, the vasodilator response to a high dose of nitroglycerin was examined. Intraarterial infusion of nitroglycerin did not significantly change mean blood pressure or heart rate in either group. Forearm blood flow response to nitroglycerin in control subjects and CHF patients did not differ significantly (Figure 1). Similarly, forearm vascular resistance during nitroglycerin was not significantly different in CHF patients and control subjects (Figures 1 and 2). To exclude hypercholesterolemia as a potential confounding factor,[13] a separate analysis was performed in 6 CHF patients with idiopathic dilated cardiomyopathy and a normal lipid profile (serum cholesterol 196 ± 4 mg%, low-density lipoprotein 124 ± 2 mg% and high-density lipoprotein 60 ± 5 mg%). Blood flow response to acetylcholine was blunted in this subset of patients (baseline 27 ± 7 ml/min and maximal acetylcholine response 34 ± 9 ml/min; p = not significant vs baseline, but $p < 0.05$ vs response to acetylcholine in control subjects), and the blood flow response to nitroglycerin was preserved (68 ± 19 ml/min). In further support of the impaired receptor-mediated arteriolar dilator response, the ratio of blood flow elicited by the maximal dose of acetylcholine and nitroglycerin was calculated in these CHF patients with a normal lipid profile. This ratio serves as a means to differentiate impaired endothelium-dependent dilation and vascular smooth muscle reactivity, and was significantly reduced in CHF patients (control subjects 0.6 ± 0.1 and patients 0.3 ± 0.09; $p < 0.05$).

Blood flow response to N-monomethyl-L-arginine: L-NMMA was administered to 6 control subjects and 6 CHF patients. The comparative percent changes obtained in the 6 subjects of each group receiving all 3 drugs in forearm blood flow and vascular resistance during acetylcholine, L-NMMA and nitroglycerin are illustrated in Figure 2. Forearm blood flow response to acetylcholine was blunted, but the response to nitroglycerin was preserved in CHF patients. L-NMMA de-

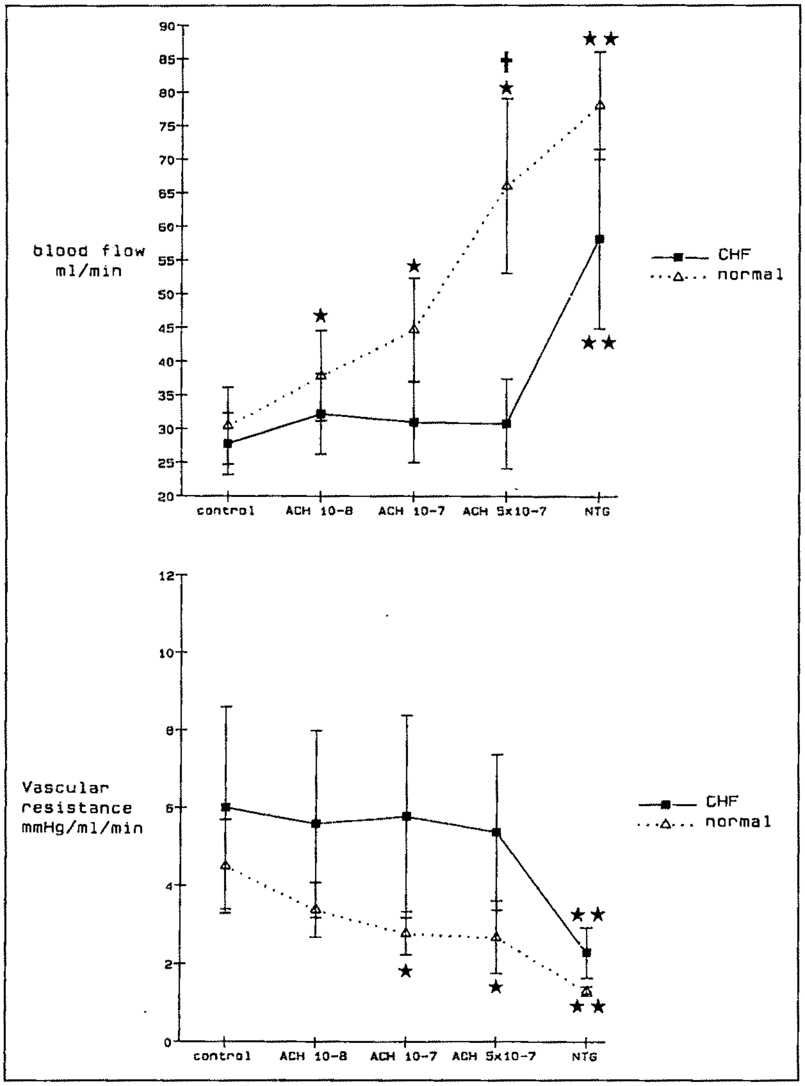

FIGURE 1. Response of forearm blood flow and vascular resistance to increasing doses of acetylcholine (ACH) (10^{-8}, 10^{-7} and 5×10^{-6} M) and to nitroglycerin (NTG) (5 nM/min) infused in brachial artery in control subjects (n = 9) and all patients with severe congestive heart failure (CHF) (n = 9). Data are mean ± SEM. *$p < 0.01$ versus control; **$p < 0.001$ versus control; †$p < 0.02$, control subjects versus heart failure patients.

creased forearm blood flow from 26 ± 6 ml/min at baseline to 14 ± 4 ml/min ($p < 0.01$) in CHF patients. L-NMMA decreased forearm blood flow from 32 ± 9 ml/min at baseline to 20 ± 6 ml/min ($p < 0.05$) in control subjects. The percent change was significantly different in control subjects compared with that in CHF patients (Figure 2). Similarly, the percent change in forearm vascular resistance elicited by L-NMMA was more prominent in CHF patients than in control subjects (Figure 2).

Effects of acetylcholine, N-monomethyl-L-arginine and nitroglycerin on radial diameter: Table II summarizes the data of all patients and those with normal serum lipids. The endothelium-mediated dilation of large conduit vessels (radial artery) in response to acetylcholine was modest and not significant in control subjects and CHF patients. Nitroglycerin dilated radial diameter in both groups. The percent change in diameter elicited by nitroglycerin was more prominent in control subjects ($p < 0.01$) (Table II). Figure 3 depicts the results of 6 subjects in each group receiving all 3 agents. No significant changes in arterial diameters were noted with L-NMMA in either group.

Plasma levels of digoxin were undetectable in 2 CHF patients, and no inverse correlation was found between the plasma levels of digoxin and the endothelium-dependent response to acetylcholine in the remaining 7.

DISCUSSION

The results of our present study led to 2 major conclusions. First, the endothelium-dependent dilation in response to acetylcholine is blunted. Second, the basal release of nitric oxide derived from L-arginine is preserved or may even be enhanced in forearm resistance vessels in CHF patients.

Blood flow response to acetylcholine was substantially inhibited by L-NMMA, indicating that the vascular effect of acetylcholine can (at least in part) be attributed to the release of nitric oxide, which is consistent with previous studies.[4,6] In contrast to the blunted response

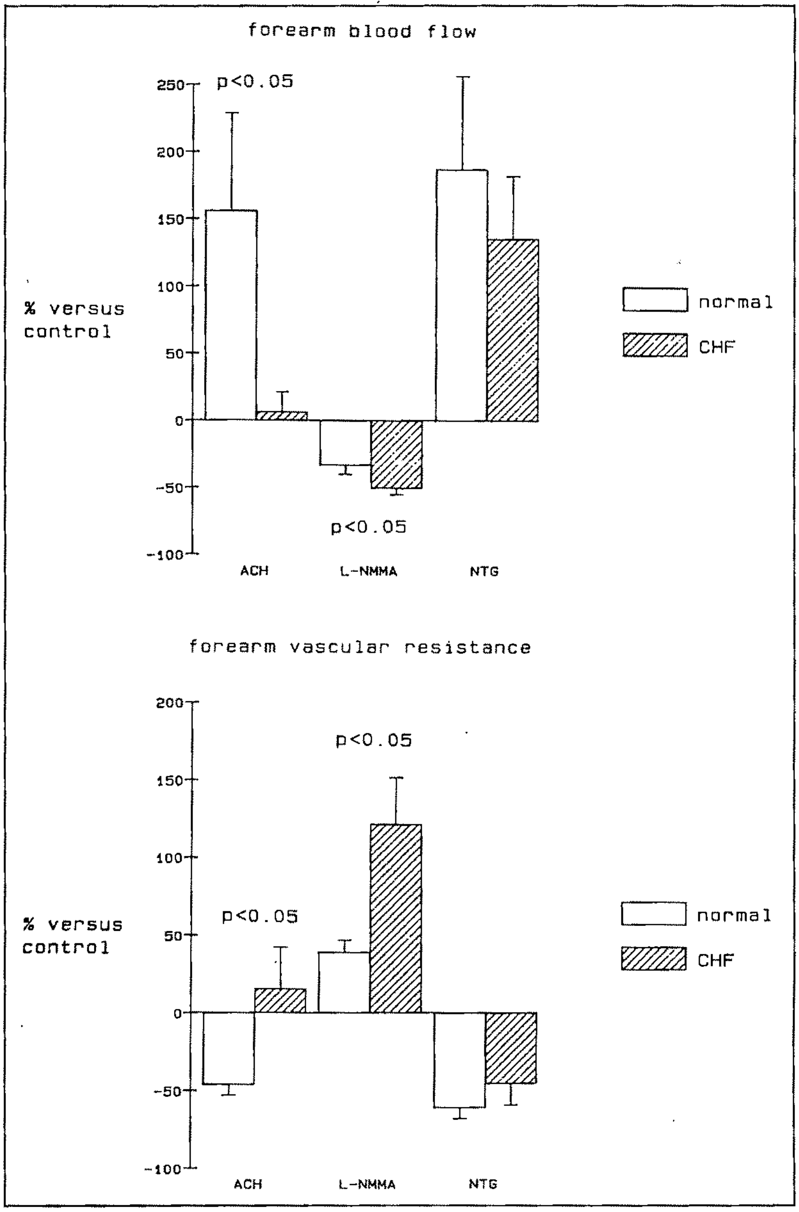

FIGURE 2. Maximal percent change in forearm blood flow and vascular resistance versus control induced by acetylcholine (ACH) (endothelium-dependent), N-monomethyl-L-arginine (L-NMMA) (inhibitor of nitric oxide synthesis) and nitroglycerin (NTG) (endothelium-independent) in control subjects (n = 6) and patients with congestive heart failure (CHF) (n = 6). Data are mean ± SEM. p values denote statistical significance between percent changes in control subjects and patients with heart failure.

TABLE II Effect of Acetylcholine and Nitroglycerin on Arterial Diameter (mm)

	Normal Subjects (n = 9)	CHF (n = 9)	CHF (LDL < 140 mg%) (n = 6)
Control 1	2.81 ± 0.1	2.84 ± 0.19	2.94 ± 0.28
ACH (10^{-8} M)	2.80 ± 0.13	2.85 ± 0.18	2.96 ± 0.26
ACH (10^{-7} M)	2.78 ± 0.13	2.83 ± 0.18	2.96 ± 0.26
ACH (5×10^{-7} M)	2.98 ± 0.12	2.88 ± 0.18	3.00 ± 0.26
NTG	3.50 ± 0.17*	3.23 ± 0.27*	3.38 ± 0.23*
ACH % change	6.7 ± 3.8	2.0 ± 1.4	2.8 ± 2.0
NTG % change	24.3 ± 0.8	14.8 ± 2.9†	16.6 ± 4.0

*$p < 0.001$ versus corresponding control values; †$p < 0.01$ versus normal subjects.

Data are mean ± SEM.

ACH = acetylcholine; CHF = congestive heart failure; LDL = low-density lipoprotein; NTG = nitroglycerin.

to acetylcholine, the increase in forearm blood flow caused by nitroglycerin was similar in CHF patients and control subjects, which is consistent with recent observations.[14] Because the dilator response to both acetylcholine and nitroglycerin involves the activation of the guanylate cyclase system (or a nonspecific effect of opposing constrictor forces), a generalized defect within the guanylate cyclase system cannot account for the present findings. Thus, in CHF patients, the stimulated release of endothelium-derived relaxing factor appears to be attenuated, resulting in an impaired endothelium-dependent relaxation of resistance vessels, which is consistent with a recent report.[15] However, this does not establish a general impairment of endothelial function, and specifically, an impairment of the basal release of nitric oxide synthetized from L-arginine. Indeed, the striking reduction in blood flow in control subjects seen after a high dose of L-NMMA was intensified rather than impaired in CHF patients, which is consistent with preliminary experimental data.[16]

This study suggests a dissociation of stimulated and basal release of nitric oxide in CHF patients (i.e., the basal release of nitric oxide appears to be preserved or may even be enhanced in the peripheral circulation, whereas the stimulated endothelial-dependent dilation exerted by acetylcholine is blunted). The observation that a substantial reduction in forearm blood flow occurred with L-NMMA in the absence of significant changes in diameters of large conductance vessels in normal subjects suggests a preferential release or activity of nitric oxide in forearm resistance vessels as compared with large conductance vessels in humans. Thus, the basal release of nitric oxide appears to have an important role in modulating tissue perfusion at the levels of distal resistance vessels in the forearm and hand, but may be negligible in conduit vessels, or alternatively, its effect on vasomotor tone in large arteries is overridden by other factors.

To establish CHF as a causal factor, other conditions associated with endothelial dysfunction such as atherosclerosis, hypercholesterolemia, hypertension and diabetes[17] should be considered. Therefore, patients with history of hypertension or diabetes were excluded. Moreover, a subgroup analysis confirmed the blunted endothelium-dependent dilation in patients with pure dilated cardiomyopathy, normal lipid profile and absence of coronary artery disease. Furthermore, the drug regimen in the CHF group (although withheld for 12 to 24 hours) may have affected endothelial function. Digoxin has been shown to impair acetylcholine-induced, endothelium-dependent relaxation.[18] However, endothelium-dependent dilation was blunted in 2 patients not receiving digoxin; furthermore, endothelium-dependent responses were not inversely related to plasma levels of digoxin. Thus, although digoxin may have contributed to the impaired endothelium-dependent dilation in some CHF patients it cannot account for the completely blunted effect of acetylcholine in these patients. To the contrary, experimental data suggest that converting enzyme inhibitors improve receptor-mediated endothelium-dependent relaxation,[19] and therefore, any residual effect of converting enzyme inhibition would tend to restore endothelial function. Indeed, it is possible that

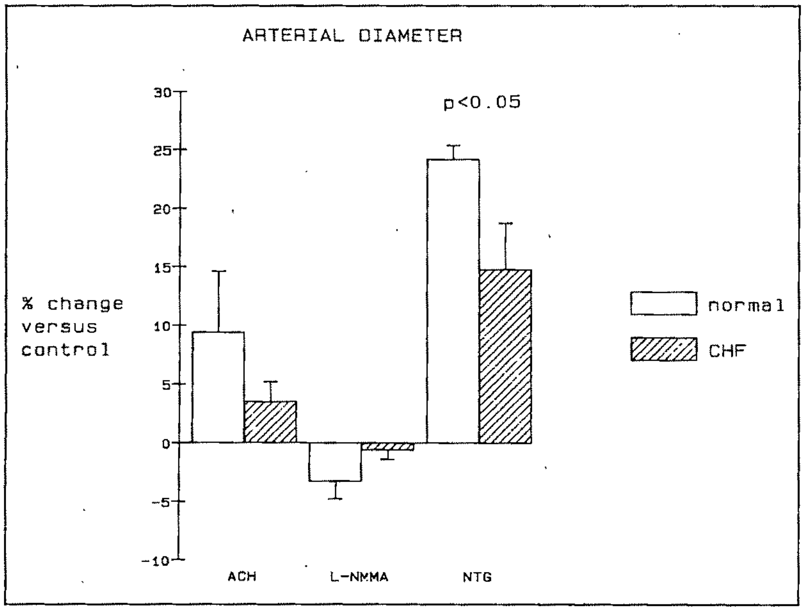

FIGURE 3. Percent change in radial arterial diameters (vs control) produced by acetylcholine (ACH) (5×10^{-7} M/min), N-monomethyl-L-arginine (L-NMMA) and nitroglycerin (NTG) in control subjects (n = 6) and patients with congestive heart failure (CHF) (n = 6). Data are mean ± SEM. p values denote statistical significance between control subjects and patients with heart failure.

long-term withdrawal of converting enzyme inhibitors would reveal a more markedly impaired endothelium-dependent relaxation in response to acetylcholine. Conceivably, specific CHF-related factors may be involved in the endothelial dysfunction of patients with CHF. Chronically reduced blood flow or tumor necrosis factor can decrease the release of endothelium-derived relaxing factor.[20,21] Thus, chronically reduced blood flow associated with limited physical activity may contribute to endothelial dysfunction in CHF patients. Plasma levels of tumor necrosis factor have been shown to be increased in patients with severe CHF[22] and, therefore, may adversely affect the vascular response to acetylcholine.[21]

The clinical feasibility of multiple interventions is limited in these patients, and, therefore, only 1 high dose of L-NMMA was administered in an attempt to achieve a maximal inhibitory effect. Significantly, the effect of L-NMMA on blood flow (−33%), and its ability to inhibit acetylcholine-induced increases in blood flow in normal subjects were similar to the maximal effects with the highest dose of L-NMMA (−32% in blood flow) used by Vallance et al[6] who noted a dose-dependent reduction in forearm blood flow with increasing doses of L-NMMA. This indicates that a high level of inhibition of nitric oxide formation was achieved in the present study by L-NMMA. The higher dose of L-NMMA in this study than that needed by Vallance may be related to the hand circulation that was not excluded to avoid movement artifacts by wrist-cuff inflation during diameter measurements.

Clinical implications: The results suggest that changes in local endothelial function may be involved in the impaired vasodilator response of the peripheral vasculature in CHF patients. The increased basal release of nitric oxide from resistance vessels may help (in a compensatory manner) to maintain adequate tissue perfusion at rest, thereby providing an important local "endogenous" vasodilator system to antagonize neurohumoral vasoconstrictor forces. However, the stimulated release of nitric oxide (i.e., during exercise) may be limited. Indeed, improvement of endothelial function could be 1 potential mechanism by which long-term converting enzyme inhibitors improve blood flow to working muscle during exercise in this setting.[23]

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VALVULAR HEART DISEASE

Long-Term (9 to 33 Months) Echocardiographic Follow-Up After Successful Percutaneous Mitral Commissurotomy

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Late results after successful percutaneous mitral commissurotomy were assessed by prospective clinical and echocardiographic follow-up. Fifty-seven patients were followed for a mean of 19 ± 6 months (range 9 to 33) after the procedure. Mitral valve area (measured by Doppler half-time method) increased from 1.0 ± 0.2 to 2.2 ± 0.5 cm^2 immediately after commissurotomy, and then decreased to 1.9 ± 0.5 cm^2 at follow-up ($p < 0.05$), whereas gradient did not change after its immediate postcommissurotomy reduction. Echocardiographic restenosis (mitral valve area ≤ 1.5 cm^2 with >50% reduction of initial gain) was seen in 12 of 57 patients (21%). Atrial shunting, detected by transthoracic color Doppler in 61% of patients immediately after the procedure (color flow jet through atrial septum), persisted in 30% at follow-up.

Restenosis by univariate analysis correlated with age, smaller valve area after the procedure, and higher echocardiographic score. Multivariate analysis identified leaflet mobility and calcifications as the components of a score that was predictive for restenosis. Magnitude of shunt (pulmonary-to-systemic flow ratio >1.5), use of a Bifoil balloon (2 balloons on 1 shaft), and smaller valve area after the procedure were predictors by multivariate analysis of the persistence of atrial shunting. Clinical improvement persisted at long-term follow-up (mean New York Heart Association class 1.6 ± 0.6 vs 2.6 ± 0.6 before commissurotomy). Improvement of ≥ 1 functional class was seen in 75% of patients (80% of those without and 58% of those with restenosis); patients with a shunt did not differ from the entire group.

Thus, percutaneous mitral commissurotomy provides excellent late (9 to 33 months) clinical results. Echocardiographic restenosis was identified in 20% of patients, and was related to age, valve morphology and a suboptimal result. Atrial shunting (small and clinically well-tolerated) was absent after long-term follow-up in 50% of patients; its persistence was related to the magnitude of the shunt, the size of the deflated balloon, and a suboptimal result.

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Percutaneous balloon mitral commissurotomy has elicited widespread interest as an alternative to surgical commissurotomy for patients with symptomatic mitral stenosis.[1–3] Although immediate results are excellent, the long-term outcome is largely unknown. Furthermore, recent reports[4,5] indicated that a significant number of patients develop small left-to-right shunts after commissurotomy as a consequence of the transseptal approach. The fate of such defects is still a subject of debate. This study assesses the long-term outcome of successful percutaneous mitral commissurotomy by echocardiography, evaluates the prevalence of echocardiographic restenosis and atrial shunting after the procedure, and identifies predictive factors for these 2 events.

METHODS

Patients: From March 1987 to April 1989, 113 percutaneous mitral commissurotomies were performed in 110 patients with a success rate of 73% (82 patients), and an incomplete success rate (mitral valve area ≤ 1.5 cm^2 or <25% increase, or both) of 19% (21 patients). In 7 patients, commissurotomy was not performed owing to technical failure, or inability to place or stabilize the balloons across the mitral valve, and in 3 patients, the procedure could not be evaluated because of major complications (2 cardiac tamponades and 1 massive mitral regurgitation). In-hospital mortality (30 days) occurred in 3 patients with multisystemic failure (48 hours after the procedure in a 79-year-old, 24 hours after an emergency mitral valve replacement and repair of left ventricular perforation in a 73-year-old, and at day 2 in a 58-year-old with a massive cerebrovascular accident).

The study group comprised 57 patients (52 women and 5 men, mean age 52 years, range 23 to 78) who underwent successful percutaneous mitral commissurotomy and were able to have echocardiographic follow-up in our institution. Clinical status at follow-up did not differ from that of the original cohort. Echocardiographic and color Doppler examinations were performed before, within 48 hours after, and at 6 and 9 to

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33 (mean 19 ± 6) months after the procedure. Before the procedure, 24 patients were in New York Heart Association functional class II, 29 were in class III, and 4 were in class IV. Previous surgical commissurotomy was performed in 11 patients. Thirty-eight patients were in sinus rhythm, 17 were in atrial fibrillation, and 2 were pacemaker-dependent. Twenty-five patients were receiving long-term anticoagulant therapy.

Cardiac catheterization and commissurotomy: As previously reported,[5] all patients underwent diagnostic left and right heart catheterization before the procedure. Pressures, blood oxygen saturation and indicator dilution curves were obtained. Cardiac output was determined by Fick and indicator dilution methods. After transseptal puncture, simultaneous left atrial and ventricular pressures were measured to document mitral valve gradient. Mitral valve area was calculated according to the Gorlin formula.[6] Dilatation of the valve was performed with 1 balloon in 1 patient, 2 balloons over 2 wires in 31 patients, and 2 balloons on 1 shaft (Bifoil, Schneider) using 1 wire in 25 patients. Mean number of inflations was 4 ± 2, and mean total duration of inflation was 31 ± 16 seconds. After the procedure, all hemodynamic measurements were repeated, including determination of transvalvular gradient. Cine left ventriculography in the right anterior oblique view was performed to assess mitral regurgitation. Atrial shunting was diagnosed by dilution curves and quantified by oxymetry. The first 38 consecutive patients from the study group were recatheterized at 6 months with a complete hemodynamic restudy.

Echocardiography: Two-dimensional and Doppler echocardiography were performed in all patients before, within 48 hours after, and at 6 and an average of 19 ± 6 (range 9 to 33) months after the procedure. Either a Hewlett-Packard 77020A ultrasound imager or a Sonos 1000 Hewlett-Packard imager (both equipped with a 2.5 MHz phased array transducer) were used. Standard echocardiographic views were obtained in all patients, including subcostal and left parasternal 4-chamber views to better visualize the atrial septum. Gain setting for color flow imaging was adjusted by initially reducing the gain to zero, and thereafter progressively increasing it until background noise appeared in addition to normal flow.

A successful procedure was defined as one with a final mitral valve area >1.5 cm^2 and a >25% increase. Echocardiographic restenosis was defined as a mitral valve area $\leq$1.5 cm^2, with a >50% reduction of the initial increase.

All data were recorded on videotape and reviewed for subsequent analysis by $\geq$2 independent observers. Mitral valve area was calculated by the pressure half-time method[7] from the continuous mitral flow velocity profile, averaging 5 beats in patients in sinus rhythm, and $\geq$10 beats in those with atrial fibrillation, with a variability of 0.100 cm^2 (0.089 cm^2 in sinus rhythm to 0.117 cm^2 in atrial fibrillation). Mitral regurgitation was graded on a 1+-to-4+ scale by color Doppler echocardiography according to the jet extension in the left atrium, divided in 4 segments from the atrioventricular plane to the posterior wall. The Wilkins echocardiographic score (from 0 to 4) was assigned for leaflet mobility, calcification, thickening and subvalvular thickening in 56 patients. The sum of the individual features provided a total echocardiographic score.[8] One patient was not sufficiently echogenic for evaluation of the score.

Statistical analysis: Mean values and SD were calculated for all clinical, echocardiographic and hemodynamic variables. Linear regression analysis was first used, followed by Student's *t* and chi-square tests. Stepwise logistic regression analysis was used to assess the predictors of restenosis and persistent atrial septal defect at long-term follow-up. The variables analyzed were age, sex, presence of previous commissurotomy, anticoagulant therapy, rhythm, calcifications on x-ray, number of months experience of the team who performed the intervention, cardiac output before and after commissurotomy, left and right atrial pressures, total pulmonary arteriolar resistances, pulmonary-to-systemic flow ratio immediately after dilatation, balloon dimensions, total duration of procedure, number of dilatations, left atrial dimension in parasternal long-axis view, mitral valve thickening and mobility, subvalvular apparatus, calcifications, total echocardiographic score, valve area calculated by pressure half-time method, and transvalvular gradient (as assessed by Doppler and mitral regurgitation) before and after commissurotomy at color Doppler examination.

A p value <0.05 was considered significant.

RESULTS

Immediate echocardiographic results: After commissurotomy, gradient decreased from 10 ± 4 to 5 ± 2 mm Hg ($p < 0.001$), and mitral valve area increased from 1.0 ± 0.2 to 2.2 ± 0.5 cm^2 ($p < 0.001$). Mitral regurgitation increased from 0.9 ± 0.5 to 1.2 ± 0.7. Before commissurotomy, 12 patients had no mitral regurgitation, 40 had 1+, and 5 had 2+. After commissurotomy, 42 patients had no change, 14 had a 1+ increase, and 1 had a 2+ increase in the degree of regurgitation.

A left-to-right atrial shunt was detected by color Doppler echocardiography in 33 of 54 patients (61%). For technical reasons, shunt scrutiny could not be performed in 3 patients.

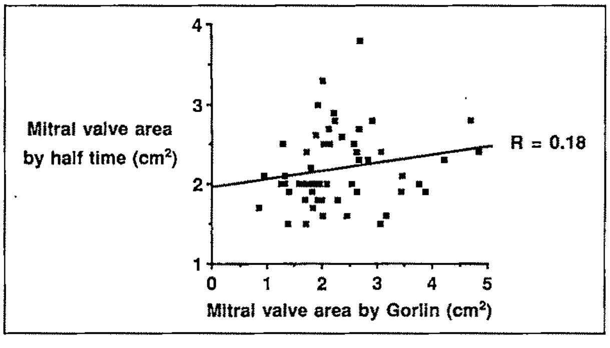

FIGURE 1. Relation between mitral valve area measured by Gorlin method and Doppler half-time immediately after valvuloplasty (r = 0.18; p = not significant).

TABLE I Predictive Factors for Restenosis by Univariate Analysis

	No Restenosis (n = 45)*	Restenosis (n = 12)	p Value
Age (yr)	49 ± 14	62 ± 9	<0.001
Valve area by echocardiography after dilatation (cm^2)	2.5 ± 0.9	1.9 ± 0.6	<0.05
Total echocardiographic score†	7.9 ± 1.4	8.9 ± 1.6	0.05
Calcifications (pts.)†			
1	17	1	
2	18	5	0.05
3	9	6	
Valve mobility (pts.)†			
1	0	1	
2	38	5	<0.005
3	6	6	
Valve thickening (pts.)†			
1	4	0	
2	38	10	NS
3	2	2	
Subvalvular apparatus (pts.)†			
1	10	2	
2	22	9	NS
3	12	1	
Valve area by catheterization after dilatation (cm^2)	2.5 ± 0.9	1.9 ± 0.6	<0.05
Pulmonary vascular resistance	184 ± 129	306 ± 263	<0.05

*n = 44 for echocardiographic characteristics.
†Wilkins echocardiographic score.[9]
NS = not significant.

Correlation with hemodynamic data: Figure 1 illustrates the correlation between echocardiographic (within 48 hours) and hemodynamic assessments of mitral valve area immediately after commissurotomy for the entire group ($r = 0.18$; p = not significant). The correlation obtained at 6 months between echocardiographic (day before) and hemodynamic data in the 38 recatheterized patients was still unsatisfactory, but improving ($r = 0.5$; $p < 0.0001$) (Figure 2). However, the correlation improved in the subgroup of 21 patients with no evidence of marked aortic or mitral regurgitation, or left atrial enlargement ≥55 mm ($r = 0.72$; $p < 0.0001$) (Figure 3).

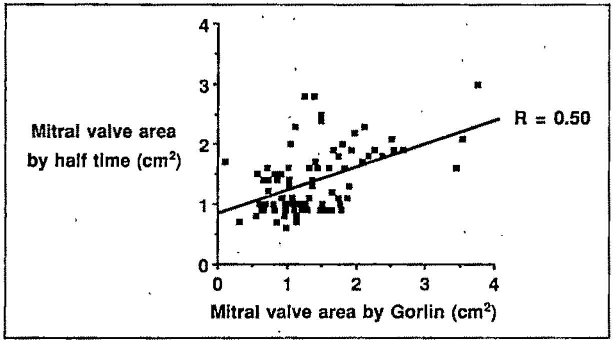

FIGURE 2. Relation between mitral valve area measured by Gorlin method and Doppler half-time using pooled data from before mitral valvuloplasty, and at 6 months in 38 recatheterized patients ($r = 0.50$; $p < 0.0001$).

A left-to-right shunt was detected immediately after commissurotomy by veno-venous dilution curves in 46 of the 54 patients (85%). Mean pulmonary-to-systemic flow ratio quantified by oxymetry was 1.3 ± 0.3; 8 patients (15%) had a ratio >1.5. The sensitivity of transthoracic color Doppler in detecting shunts was 65%, with a specificity of 63%. However, all ratios >1.5 were recognized by echocardiography.

Late echocardiographic results: At the latest follow-up (19 ± 7 months), mitral valve area decreased to 1.9 ± 0.5 cm^2 ($p < 0.05$), whereas gradient remained unchanged. Twelve of the 57 patients (21%) met the criteria for echocardiographic restenosis. Mean area was 1.3 ± 0.1 cm^2 in this group versus 2 ± 0.4 cm^2 in patients without restenosis ($p < 0.01$). Mitral regurgitation remained unchanged in 26 patients, decreased by 1+ in 18, and increased by 1+ in 12 and by 2+ in 1. Left atrial dimension decreased from 49 ± 7 mm at 48 hours after the procedure to 45.6 ± 7.5 mm at follow-up ($p < 0.05$). A left-to-right shunt through an atrial septal defect was seen in only 16 of the 54 patients (30%) compared within 33 of 54 (61%) immediately after the procedure.

Symptoms: Improvement of ≥1 New York Heart Association class was seen in 75% of patients (80% of those without and 58% of those with restenosis). Mean functional class of patients with atrial shunting did not differ from the entire group (8 in class I, 7 in class II, and 1 in class III).

Predictive factors of restenosis: Table I lists the predictors for restenosis identified by univariate analysis. Among the 20 patients aged >60 years (mean 69 ± 4), the restenosis rate was 40% compared with 11% in the 37 patients aged <60 (mean 46 ± 11). Restenosis was seen in 11 of 36 patients (30%) with an echocardiographic score ≥8 compared within only 1 of 20 (5%) with a score <8 ($p < 0.05$). When multiple logistic regression analysis was performed, leaflet mobility and calcifications were identified as the components of the score predictive for restenosis.

Factors predictive of long-term persistence of atrial shunting: Table II describes the variables correlated with persistence of atrial shunting at long-term follow-up by univariate analysis. Stepwise logistic regression analysis identified pulmonary-to-systemic flow ratio >1.5, use of Bifoil balloon, and mitral valve area after

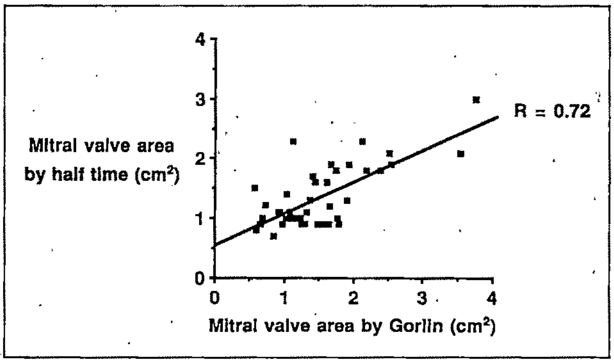

FIGURE 3. Relation between mitral valve area measured by Gorlin method and Doppler half-time in subgroup of 21 patients with no evidence of aortic valve disease, mitral regurgitation or left atrial enlargement ≥55 mm ($r = 0.72$; $p < 0.0001$).

TABLE II Predictive Factors for Persistence of Atrial Shunting by Univariate Analysis

	No Atrial Shunting (n = 38)	Atrial Shunting (n = 16)	p Value
Cardiac index (liters/min/m^2)	2.6 ± 0.8	2.0 ± 0.4	<0.01
Right atrial mean pressure (mm Hg)	4.9 ± 3.1	7.1 ± 2.6	0.01
Left atrial mean pressure (mm Hg)	11.5 ± 5	16 ± 4	<0.01
Valve area after procedure (cm^2)	2.5 ± 0.9	2.0 ± 0.6	<0.05
Duration of procedure (min)	124 ± 26	107 ± 29	<0.05
Qp/Qs >1.5 (pts.)	3 (7%)	6 (37%)	0.01
Use of Bifoil balloon (pts.)	5 (14%)	7 (45%)	0.01
Echocardiographic restenosis (pts.)	6 (15%)	6 (37%)	<0.05

commissurotomy as predictors of persistence of atrial shunting.

DISCUSSION

The results of this study indicate that successful percutaneous mitral commissurotomy for symptomatic mitral stenosis produces excellent long-term results, as assessed by echocardiography. At a mean follow-up of 19 months, the restenosis rate was 21%, and the prevalence of persistent atrial shunting was 30%. Both of these complications were well-tolerated clinically.

Echocardiographic restenosis: The echocardiographic rate of restenosis in the present study (21%) is similar to the 20% rate obtained by Abascal et al[9] in a smaller series of patients. A much lower rate was reported by Vahanian et al[10] and Al Zaibag et al[11] (Table III). This difference is likely due (at least in part) to the difference in age. The influence of age on restenosis rate is evident within our study (<60 years: 11%; and >60 years: 40%).

Morphologic alterations of the valve influence both the immediate and short-term outcomes of mitral commissurotomy.[9,12-14] In the study of Palacios et al,[12] 7 of 10 patients with an echocardiographic score >8 developed restenosis compared with only 1 of 27 with a score ≤ 8. Analysis of the individual components of the score revealed that valve mobility and calcification were the strongest predictors of a poorer long-term outcome. A suboptimal result of commissurotomy (characterized by smaller valve area immediately after the procedure) was also an independent predictor of restenosis.

The rate of restenosis up to 10 years after surgical commissurotomy has been estimated at between 10 and 28%. As with percutaneous commissurotomy, the results after surgical commissurotomy are worse in the presence of severe morphologic alterations of the valve.[15-17] A comparison of the long-term results of the 2 procedures cannot be accurately made, because no similar echocardiographic studies have been performed before surgical commissurotomy, and the criteria for restenosis differ.[18,19] However, the clinical improvement up to 33 months after percutaneous commissurotomy is similar to that after surgery.

TABLE III Restenosis and Clinical Improvement

Investigators	Pts.	Mean Age	Months of Follow-Up	Restenosis Rate	Improvement of ≥1 NYHA Class
Abascal et al[10]	20	52	7.5	20%	
Vahanian et al[11]	91	43	9	4%	96%
Al Zaibag et al[12]	41	26	12	0%	90%
Desideri et al	57	52	19	21%	75%

NYHA = New York Heart Association.

Atrial shunting: An atrial septal defect with a left-to-right shunt was detected by transthoracic color Doppler echocardiography in 61% of patients within 48 hours after commissurotomy, but was absent in 50% of them at long-term follow-up. The presence of a left-to-right shunt at long-term follow-up correlated with restenosis in our study, reproducing the components of the Lutembacher syndrome.[20]

Signs of more severe, long-standing disease before commissurotomy (characterized by higher left and right atrial pressures, and a lower cardiac index) correlated with persistence of an atrial shunt. With heavy alteration of the mitral apparatus, commissural splitting is thus more difficult, and the balloon moves toward the septum during inflations, causing a prolonged sawing motion of the catheter shaft and enlargement of the septal defect.[21]

Clinical status: At follow-up, most patients had milder symptoms than before commissurotomy. The improvement of ≥1 functional class in 75% of our patients at 19 months is similar to the findings of Palacios et al[12]; 80% of their patients improved at follow-up. More improvement has been reported in European and North African patients[10,11] (Table III), probably due in part to the younger age. In our series, 86% of patients aged <60 years improved compared with 65% of those aged >60 years. Echocardiographic restenosis was associated with a worse functional class, but the presence of a shunt did not influence the clinical status.

Study limitations: In our series, valve area was assessed by means of the pressure half-time method. The correlation between hemodynamic and echocardiographic measurements was poor before commissurotomy and at 6 months (Figure 2); these measurements were pooled to minimize the greater spread after commissurotomy. This must be partly related to the absence of simultaneous measurements (24- to 48-hour difference), but other factors are likely involved also. Calculation of valve area by the Gorlin formula has a margin of error up to 20%, especially in patients with associated mitral regurgitation[22] and atrial shunting; therefore, it is not an ideal gold standard.

The pressure half-time method can also be suboptimal in cases with associated valve disease.[23] In patients with no evidence of marked aortic or mitral regurgitation, or severe left atrial enlargement, the correlation with hemodynamic measurements improved considerably. Other investigators also reported poor correlations between echocardiographic and hemodynamic measurements.[24-26]

Transthoracic color flow Doppler echocardiography has the advantages of being noninvasive and easily repeatable. Its sensitivity in detecting atrial shunting within 48 hours after commissurotomy was 65%, with a specificity of 63%, compared with the postprocedure veno-venous dilution technique. This sensitivity would have been surely increased by using contrast echocardiography together with provocative maneuvers. Controversy exists as to whether false-positive color flow Doppler studies may in fact be false-negative indicator dilution tests or otherwise indicate the existence of early shunt disappearance. In either case, color flow mapping is the most accurate method for noninvasive assessment of interatrial defects.

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Methodologic Issues in Clinical Evaluation of Stenosis Severity in Adults Undergoing Aortic or Mitral Balloon Valvuloplasty

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Although both catheterization and Doppler measures of valvular stenosis severity have been validated, each has specific advantages and limitations, particularly in the setting of balloon valvuloplasty. Invasive valve area and mean pressure gradient recorded immediately before and after aortic (n = 589) or mitral (n = 608) catheter balloon valvuloplasty were compared with Doppler valve area and mean pressure gradient recorded <30 days before and 24 to 72 hours after the procedure.

For aortic stenosis, Doppler valve area ranged from 0.1 to 1.4 cm^2 before and 0.2 to 2.3 cm^2 after catheter balloon valvuloplasty. Doppler and invasive aortic valve areas differed by $\leq$0.5 cm^2 in 99% and by <0.2 cm^2 in 92% of patients. Linear correlation was higher before versus after catheter balloon valvuloplasty, for both valve area ($r = 0.49$ vs $r = 0.35$, $p = 0.01$) and mean pressure gradient ($r = 0.64$ vs $r = 0.50$, $p = 0.01$). Group mean invasive valve area was slightly smaller before (0.50 vs 0.59 cm^2, $p < 0.0001$) but was not different after (0.80 vs 0.78 cm^2, $p = 0.16$) catheter balloon valvuloplasty. Variables affecting the valve area differences were cardiac output, aortic regurgitation, heart rate and blood pressure. Mean pressure gradient differences were related to echo quality, blood pressure and mitral regurgitation.

For mitral stenosis, 2-dimensional echocardiographic valve area ranged from 0.4 to 2.8 cm^2 before and 0.7 to 3.8 cm^2 after catheter balloon valvuloplasty. Two-dimensional echocardiography and invasive mitral valve areas differed by $\leq$0.5 cm^2 in 96% and by <0.2 cm^2 in 81% of cases. Linear correlation was not different before versus after catheter balloon valvuloplasty for two-dimensional echocardiographic valve area ($r = 0.40$ vs 0.36), pressure halftime valve area ($r = 0.31$ vs 0.32) or mean pressure gradient ($r = 0.55$ vs $r = 0.46$). Group mean 2-dimensional echocardiography and pressure halftime valve areas were larger than invasive valve areas before (1.09 vs 1.02 cm^2, $p = 0.001$) and smaller after (1.71 vs 2.02 cm^2, $p < 0.0001$) catheter balloon valvuloplasty. Important variables affecting the differences were mitral regurgitation, interatrial shunt, cardiac output and heart rate.

Nonsimultaneous studies, differing volume flow measurements, and the underlying accuracy of each technique largely account for discrepancies between these methods. The clinical use of each will depend on its ability to predict long-term patient outcome.

(Am J Cardiol 1992;69:1607–1616)

The National Heart, Lung, and Blood Institute (NHLBI) Balloon Valvuloplasty Registry enrolled adults undergoing percutaneous balloon valvuloplasty at 24 medical centers between November 1, 1987 and October 31, 1989. To assess immediate efficacy of the procedure, invasive measures of stenosis severity were recorded immediately before and immediately after balloon dilation. Because sequential invasive measurements were not feasible for long-term follow-up in this population, Doppler echocardiographic measures of stenosis severity also were recorded before and after the procedure to provide a baseline for long-term noninvasive follow-up.

Although both catheterization[1-6] and Doppler[7-18] measurements of stenosis severity have been well validated, each has specific advantages and potential limitations, particularly in the setting of balloon valvuloplasty.[19-30] In addition, discrepancies between catheterization and Doppler data may be due to several factors including individual expertise, measurement technique, intervening physiologic changes, and the underlying accuracy of each method. To examine the importance of each of these factors in the setting of routine clinical data collection, we compared invasive and noninvasive measures of stenosis severity in the Balloon Valvuloplasty Registry.

METHODS

Patient population: The study population included 589 adults undergoing balloon aortic valvuloplasty with both catheterization and paired pre- and postvalvuloplasty Doppler studies. Mean age was 78 years (range

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*See Appendix for Balloon Valvuloplasty Registry list.

24 to 103); 57% were women.[31] Mitral stenosis data were compared in 608 adults undergoing mitral valvuloplasty. Mean age was 54 years (range 23 to 86); 19% were men and 81% were women.[32]

Catheterization data: All measurements were obtained immediately before and immediately after the valve dilation by the invasive cardiologist at each clinical site.

AORTIC STENOSIS: Left ventricular and ascending aortic pressures were recorded using micromanometer-tipped or fluid-filled catheters either with 2 separate catheters (simultaneous pressures) or by pullback withdrawal of the catheter from the ventricle to the aorta (nonsimultaneous). When peripheral arterial pressure was used, the degree of peripheral amplification was taken into account by measuring the difference between ascending aortic and peripheral arterial pressure.[5] Mean transaortic pressure gradient was calculated as the systolic area between the pressure curves divided by the systolic ejection period. Transaortic volume flow was assumed to be equal to cardiac output measured using either the Fick (n = 34%), thermodilution (n = 57%) or green-dye (n = 10%) method. Aortic valve area was calculated using the formula of Gorlin and Gorlin (n = 98%)[1,2] or by the Hakki formula (n = 2%).[3]

MITRAL STENOSIS: Left ventricular and left atrial pressures were recorded using fluid-filled catheters, with left atrial pressure measured directly by the transseptal approach. Mean transmitral gradient was calculated from the diastolic area between the curves divided by the diastolic filling period. Transmitral volume flow was assumed to equal cardiac output and was measured by Fick (45%), thermodilution (50%), or green-dye (5%) techniques. Mitral valve area was calculated with the Gorlin and Gorlin formula, with an empiric constant of 40.[4] An atrial septal defect was considered present after the procedure if the left-to-right shunt (calculated from oxygen-saturation data) was ≥0.5 liters/min.

Doppler echocardiography: The prevalvuloplasty Doppler echocardiogram was recorded within 30 days before the procedure in 96% of patients (mean interval 3 ± 6 days). The postvalvuloplasty echo-Doppler study was performed 24 to 72 hours after the procedure (mean interval 38 ± 20 hours). Blood pressure and heart rate were recorded at the time of each echo-Doppler study. The echo-Doppler study was interpreted by an observer at each center. Standardized techniques for echocardiography were discussed and chosen at organized meetings of the echocardiographers from each site.

AORTIC STENOSIS: The aortic stenosis jet was recorded with continuous-wave Doppler. The highest frequency signal recorded from any window (apical, right parasternal, and so forth) was considered to represent the most nearly parallel intercept angle between the direction of blood flow and the ultrasound beam and was used for all subsequent calculations. Maximal velocity and mean gradient were averaged from 3 to 5 good quality beats in normal sinus rhythm, and from 5 to 10 consecutive beats in atrial fibrillation. Mean transaortic pressure gradient was determined by integration of instantaneous pressure gradients throughout systole using either the measurement package in the ultrasound system or an off-line analysis system.

Left ventricular outflow tract internal diameter was averaged from 3 to 5 beats using the 2-dimensional parasternal long-axis image in midsystole. Diameter was measured from the endocardial septal echo to the leading edge of the anterior mitral leaflet echo, just below the aortic valve and parallel to the valve plane. Outflow tract cross-sectional area was calculated as $\pi(D/2)^2$.

Left ventricular outflow tract flow was measured from either an apical 4-chamber view angulated anteriorly or an apical long-axis view using conventional pulsed Doppler with the sample volume positioned just below the region of the flow acceleration into the aortic jet.

Aortic valve area was calculated using either the conventional continuity equation[13-18] using velocity time integrals for the outflow tract and aortic velocity signals (14%), or the simplified continuity equation[14,33] using maximal velocities (86%).

Aortic regurgitation was evaluated either with conventional pulsed Doppler echocardiography using a small sample volume (1.5 to 3 mm) with 2-dimensional guided mapping of the flow disturbance in the left ventricle in ≥2 orthogonal planes or with color Doppler flow imaging.[34]

MITRAL STENOSIS: The mitral stenosis jet was recorded from an apical approach, using either continuous-wave, conventional pulsed, or high pulse-repetition-frequency Doppler. Care was taken to obtain a tonal signal with a smooth velocity envelope of flow in diastole and a well-defined peak early diastolic velocity and the early diastolic slope. Mean gradient was derived by integration of instantaneous pressure gradients throughout diastole (using either the measurement package on the instrument or an off-line system) averaged from 3 to 5 consecutive beats in normal sinus rhythm and 5 to 10 consecutive beats in atrial fibrillation. The mitral valve area by the pressure halftime method[6,8-10] was averaged from 3 to 5 good quality beats.

Mitral regurgitation was assessed in ≥2 tomographic planes using conventional pulsed Doppler or color flow imaging, or both.[34]

Two-dimensional cross-sectional area of the mitral orifice was determined from short-axis views obtained by scanning from the left ventricular apex slowly up to the mitral valve to determine the minimal orifice area.[7] Care was taken to set the gains at minimal levels and to trace the inner edge of bright echos to determine the mitral orifice in cm².

Statistical analysis: Catheterization and Doppler data were compared by several statistical approaches:

1. *Linear regression with calculation of Pearson's correlation coefficient.* The limitation of this approach was the narrow range of data in the study population, since linear regression assumes that a representative range of data are included.

2. *The group mean of the numerical differences between catheterization and Doppler measures.* This approach allows comparison of various subgroups to identify factors that increase the discrepancy between the 2 methods.

3. *Univariate analysis.* Correlations were transformed to the normal distribution and compared by a test of equality of means of independent normals.[35] Means were compared by the *t* test and by regression analysis.

4. *Multivariate analysis.* The multivariate analyses were performed in steps since all of the covariate data were not available for each patient. First univariate analyses were performed for all covariates of interest. Covariates with univariate $p < 0.10$ were used in a step-

TABLE I Correlations Between Catheterization and Doppler Echocardiographic Measures of Aortic Stenosis Severity

	Valve Area		Mean Gradient	
	Before	After	Before	After
Entire group	0.49 (462)*	0.35 (467)	0.63 (543)	0.30 (549)
Echo quality				
Excellent	0.58 (88)	0.30 (75)	0.72 (91)	0.62 (71)
Acceptable	0.47 (363)	0.36 (379)	0.63 (425)	0.49 (450)
Time after procedure				
0–24 hours (156)		0.42 (193)		0.47 (214)
24–48 hours (122)		0.43 (145)		0.53 (172)
>48 hours (59)		0.19 (78)		0.49 (97)

*The number of patients for each correlation is shown in parentheses.

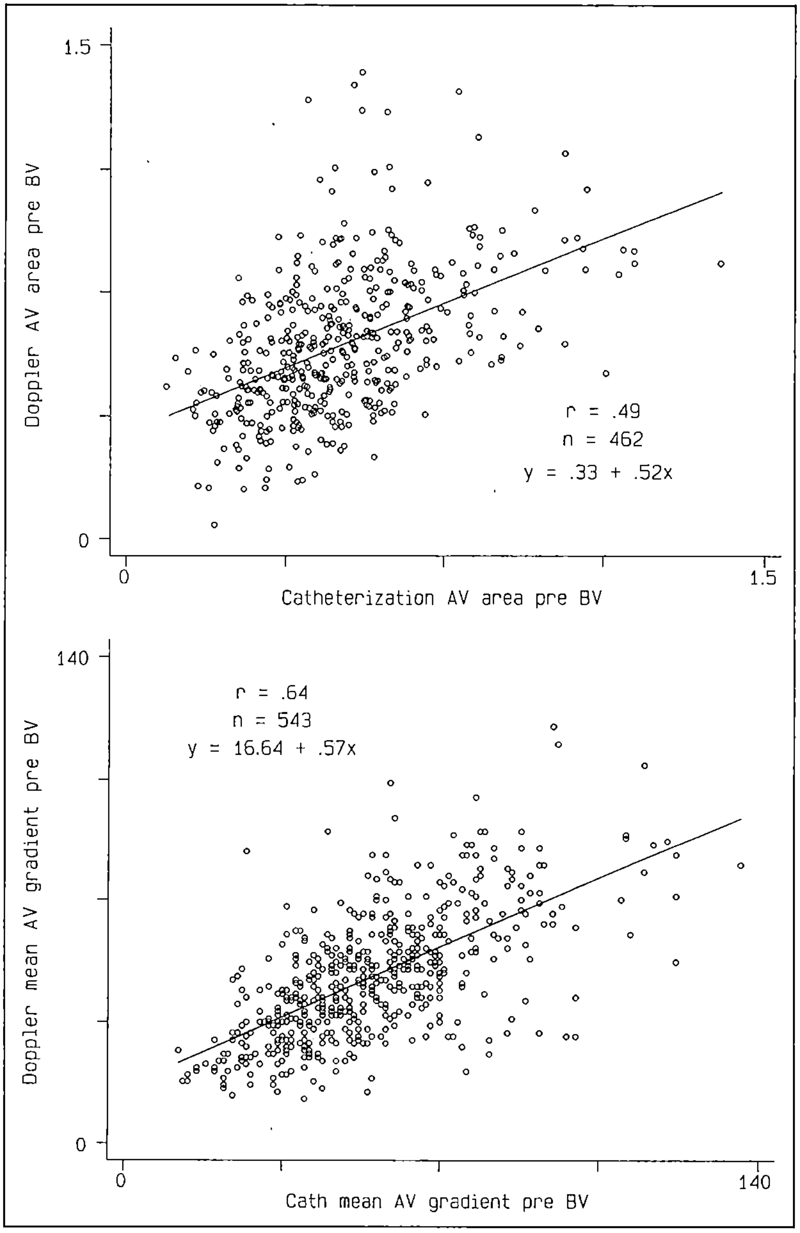

FIGURE 1. Aortic stenosis: Linear regression comparing invasive versus noninvasive valve areas *(top)* and transaortic pressure gradients *(bottom)* for the entire group before the procedure. AV = aortic valve; BV = balloon valvuloplasty.

TABLE II Group Mean ± SD of Catheterization and Doppler Echocardiographic Measurements of Aortic Valve Area and Gradient

	No. of Pts.	Cath.	Echo.	Difference	p Value
Area (cm^2)					
Before	462	0.50 (0.200)	0.59 (0.21)	−0.08 (0.21)	<0.0001
After	467	0.80 (0.311)	0.782 (0.29)	0.02 (0.34)	0.16
Gradient (mm Hg)					
Before	543	54.9 (20.3)	47.8 (18.1)	7.1 (16.4)	<0.0001
After	549	29.3 (12.9)	36.0 (15.1)	−6.7 (14.1)	<0.0001

Standard deviations are shown in parentheses.
Cath. = catheterization; Echo. = echocardiography.

TABLE III Differences ± SD of the Difference Between Catheterization and Doppler Measurements of Aortic Valve Area in Relation to Severity of Aortic Regurgitation

	None	Mild	Moderate
Area before*	−0.03 ± 0.21 (93)	−0.08 ± 0.21 (273)†	−0.15 ± 0.20 (85)†
Area after*	0.08 ± 0.34 (92)†	0.04 ± 0.35 (250)	−0.07 ± 0.33 (108)†
Gradient before	8.64 ± 16.43 (118)†	6.34 ± 16.43 (319)†	7.20 ± 17.02 (93)†
Gradient after	−5.51 ± 13.04 (110)†	−6.72 ± 14.14 (298)†	−8.28 ± 14.33 (121)†

*Significant linear trend, $p < 0.05$.
†Significantly different from zero, $p < 0.05$.
The number of patients in each subset is shown in parentheses. Differences are catheterization minus Doppler measurements of valve area or pressure gradient.

wise analysis with forward selection to determine the group of covariates with strongest multivariate relation to the outcome. The selection process stopped when no remaining unselected variable had $p < 0.05$. Finally, to maximize the number of patients for the regression model, the variables selected by the stepwise process were used in a multivariate regression to determine the final model.

RESULTS

Aortic stenosis (Figure 1): Doppler and invasive aortic valve areas ranged from 0.1 to 1.4 cm^2 before the procedure. Postprocedure Doppler valve areas ranged from 0.2 to 2.3 cm^2 and invasive aortic valve areas from 0.1 to 2.7 cm^2. Mean transaortic pressure gradient ranged from 13 to 120 mm Hg before and from 3 to 104 mm Hg after the procedure.

Of note, heart rate at the time of catheterization differed ($p < 0.0001$) from heart rate at the time of echocardiography (82.0 vs 78.7 beats/min). Similarly, peak systolic blood pressure differed between the 2 studies (132 vs 125 mm Hg, $p < 0.0001$).

Correlations for catheterization and Doppler data are highest for measurements before the procedure (Table I). Echocardiograms recorded as "excellent" quality generally had higher correlations with catheterization measurements than did echocardiograms recorded as "acceptable" quality.

The group mean catheterization and Doppler measurements of valve area and mean gradient are listed in Table II. Before the procedure, Doppler valve area was significantly larger than catheterization valve area ($p < 0.0001$) but there was no significant difference after the procedure ($p = 0.25$). The increase in aortic valve area from before to after the procedure was 0.29 ± 0.18 cm^2 by catheterization and 0.19 ± 0.19 cm^2 by Doppler ($p < 0.0001$).

VALVE AREA: Factors that might influence aortic valve area measurements were examined for their effect on the magnitude of the difference between catheterization and echocardiography measurements. Cardiac output had the most important effect on the differences in measured valve areas both before and after valvuloplasty ($p < 0.001$), with higher outputs associated with relatively larger catheterization area measurements. The degree of aortic regurgitation measured at echocardiography also was important ($p = 0.001$), with Doppler valve areas being relatively larger for greater degrees of regurgitation (Table III). A higher heart rate at the time of valvuloplasty was associated with slightly larger Doppler measurements ($p < 0.02$). When all variables, including those not significant univariately, were used in a stepwise model, cardiac output and heart rate at catheterization were the only variables that remained significant both before and after valvuloplasty.

Note that Doppler and invasive aortic valve areas differed by ≤ 0.5 cm^2 in 99% and by < 0.2 cm^2 in 92% of patients.

PRESSURE GRADIENT: Before the procedure, the catheterization gradient was significantly larger ($p < 0.0001$); after the procedure the catheterization gradient was significantly smaller ($p < 0.0001$). The decrease in gradient was 26 ± 16 mm Hg by catheterization and 12 ± 14 mm Hg by Doppler ($p < 0.0001$).

The difference between catheterization and echocardiographic transaortic pressure gradient measurements primarily was influenced by quality of the echocardiogram, with less difference in the gradient measurements for echocardiograms rated as excellent quality ($p < 0.006$). Mitral regurgitation was associated with relatively larger Doppler gradients before valvuloplasty ($p = 0.001$). After valvuloplasty, higher aortic diastolic pressure at the time of echocardiography was associated with relatively lower Doppler areas ($p = 0.001$). Other

FIGURE 2. Mitral stenosis: Comparison of invasive versus noninvasive 2-dimensional valve areas *(top)*, halftime valve areas *(middle)* and mean transmitral pressure gradient *(bottom)* for the entire group before the procedure. MC = mitral commissurotomy; MV = mitral valve; T 1/2 = pressure halftime.

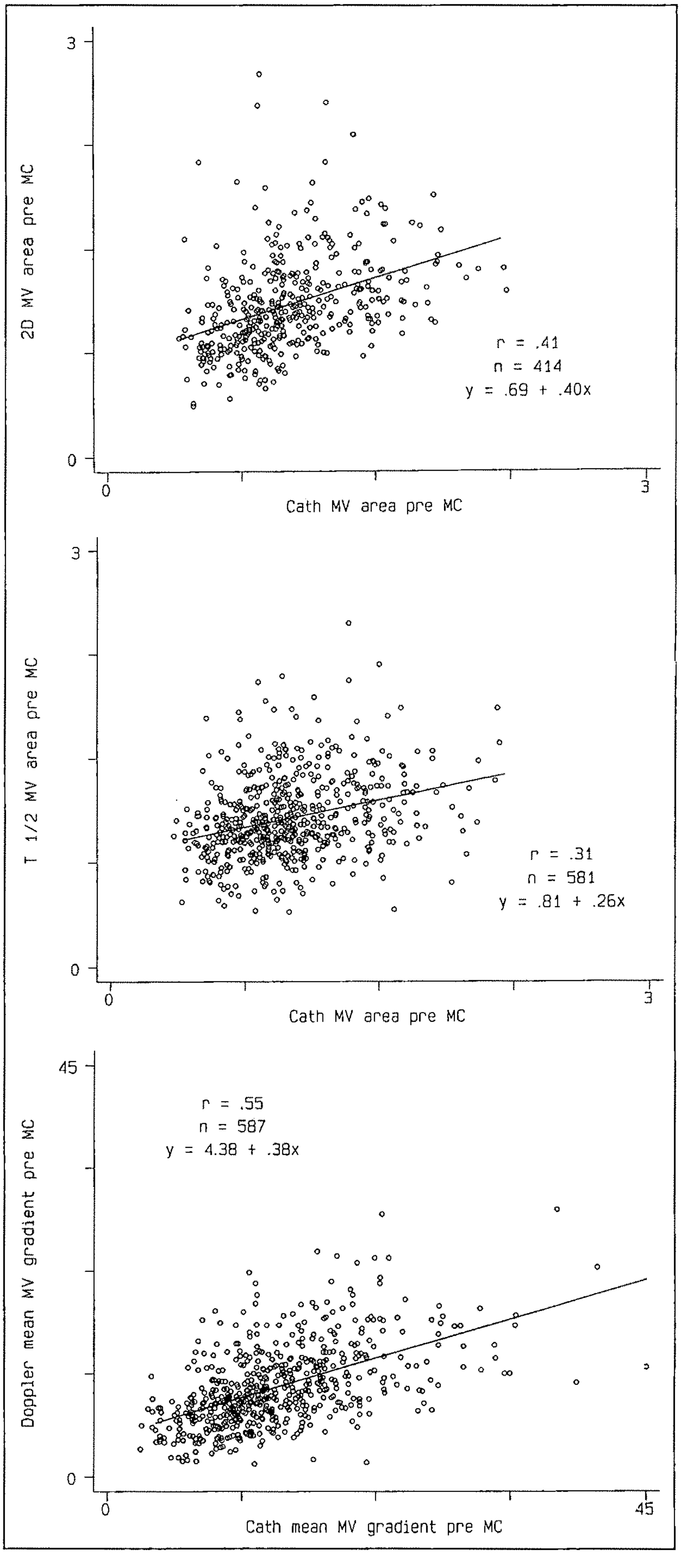

TABLE IV Correlations Between Catheterization and Doppler Echocardiographic Measurements of Mitral Stenosis Severity

	Correlation Coefficient					
	2-D Area		T ½ Area		Gradient	
	Before	After	Before	After	Before	After
Entire group	0.41 (414)	0.38 (409)	0.31 (581)	0.33 (523)	0.55 (587)	0.46 (568)
Time after procedure						
0–24 hours		0.32 (127)		0.37 (165)		0.48 (178)
24–48 hours		0.41 (144)		0.28 (196)		0.49 (200)
>48 hours		0.54 (37)		0.42 (67)		0.43 (68)
Mitral regurgitation						
0–1+	0.40 (356)	0.42 (294)	0.30 (491)	0.35 (373)	0.54 (497)	0.45 (404)
≥2+	0.44 (57)	0.23 (114)	0.36 (86)	0.26 (148)	0.62 (86)	0.46 (161)
Shunt						
Present		0.32 (96)		0.29 (122)		0.55 (133)
Absent		0.38 (285)		0.34 (351)		0.42 (383)

*The numbers in parentheses are the numbers of patients in that group.
Before/after = correlation between invasive and noninvasive data before or after the valvuloplasty procedure.
T ½ = Doppler halftime method for mitral valve area determination; 2-D = two-dimensional echocardiographic mitral valve area.

TABLE V Mean ± SD of Catheterization and Echocardiography Measurements of Mitral Valve Area and Gradient

	No. of Pts.	Cath.	Echo.	Difference
2-D area (cm^2)				
Before	414	1.02 (0.34)	1.09 (0.33)	−0.08 (0.37)*
After	409	2.02 (0.82)	1.71 (0.45)	0.31 (0.77)*
Pressure half-time area (cm^2)				
Before	581	1.00 (0.34)	1.07 (0.29)	−0.07 (0.37)*
After	523	1.96 (0.79)	1.76 (0.49)	0.20 (0.78)*
Gradient (mm Hg)				
Before	581	14.11 (6.18)	9.76 (4.29)	−4.35 (5.24)*
After	568	6.02 (3.18)	5.43 (2.54)	−0.58 (3.03)*

*Different from zero, $p < 0.0001$.
Abbreviations as in Tables II and IV.

factors that influenced the difference after valvuloplasty were heart rate at catheterization ($p = 0.03$), aortic peak systolic pressure at echocardiography ($p = 0.02$), aortic diastolic pressure at catheterization ($p = 0.02$) and age ($p = 0.02$). In a stepwise regression analysis using all variables, the quality of the echocardiogram was significant both before and after valvuloplasty. Mitral regurgitation also was important before valvuloplasty, and aortic diastolic pressure at echocardiography was significant after the procedure.

Mitral stenosis (Figure 2): Two-dimensional echocardiographic mitral valve area ranged from 0.4 to 2.8 cm^2 before and 0.7 to 3.8 cm^2 after the procedure. Pressure halftime valve area range was 0.5 to 2.4 cm^2 before and 0.6 to 4.0 cm^2 after the procedure. Invasive mitral valve area was 0.4 to 2.2 cm^2 before and 0.5 to 6.0 cm^2 after the procedure. Doppler mean gradient ranged from 2 to 28 mm Hg before and from 1 to 19 mm Hg after the procedure. Heart rate and aortic peak systolic pressure differed between catheterization and echocardiography (82.0 vs 74.2 beats/min and 128.8 vs 121.6 mm Hg).

For the entire study group, there was no difference in the correlation between invasive and noninvasive measurements of stenosis severity before or after the procedure (Table IV) or for correlation between 2-dimensional echocardiography and halftime valve areas ($r = 0.61$ before and $r = 0.54$ after the procedure). There was no consistent relation between echo quality and correlation between invasive and noninvasive data.

Correlations for the 2-dimensional echocardiographic valve area increased with time after the procedure, whereas the correlation for halftime valve area was not affected over the time interval studied. Mitral regurgitation ≥2+ was associated with a poorer correlation for the halftime and 2-dimensional areas after the procedure. The presence of an interatrial shunt after the procedure decreased the correlations for 2-dimensional and halftime areas.

The differences between noninvasive and invasive measures of mitral stenosis severity are listed in Table V. The noninvasive valve areas are slightly larger than invasive areas before, and slightly smaller than invasive areas after the procedure. The increase in mitral valve area after the procedure was 0.96 ± 0.69 cm^2 at catheterization versus 0.62 ± 0.44 cm^2 by 2-dimensional echocardiography and 0.68 ± 0.48 cm^2 by the halftime methods (both $p < 0.0001$). Mean pressure gradient decreased by 8 ± 6 mm Hg at catheterization and by 4 ± 4 mm Hg with Doppler echocardiography ($p < 0.0001$).

Factors that might be related to the difference in echocardiography and catheterization mitral stenosis measurements were examined by univariate and multivariate analysis. The most important factor influencing the differences in measured mitral areas and gradients was cardiac output. Increased cardiac outputs were associated with relatively higher catheterization measurements of valve area and relatively lower catheterization valve gradients. Increased heart rate during echocardiography was associated with higher 2-dimensional echocardiographic and pressure halftime area measurements both before and after the procedure ($p = 0.03$ to $p < 0.001$), as were older age and higher blood pressures in the area measurements before valvuloplasty ($p = 0.04$ to $p < 0.001$). Mitral regurgitation measured by

Doppler was associated with larger echocardiography area measurements after valvuloplasty. The presence of an interatrial shunt decreased the catheterization valve area relative to the pressure halftime area measurement ($p = 0.004$), but the difference for the 2-dimensional area measurements was not statistically significant ($p = 0.65$). Increased heart rate during catheterization was associated with a lower catheterization gradient relative to the echo gradient ($p < 0.001$). The time between the procedure and the echocardiogram did not significantly affect the difference in measured areas and gradients ($p = 0.11$ to 0.54).

All variables were used in stepwise analyses of the differences. Cardiac output was the most important variable for 2-dimensional echocardiography and pressure halftime areas measured before and after-valvuloplasty. In 3 of the area analyses, heart rate at the time of echocardiography also was significant. The only other significant variable was systolic blood pressure at the time of valvuloplasty in the 2-dimensional echocardio-

TABLE VI Selected Previous Studies of Valve Area Determination

Reference	Comparison	No. of Pts.	Study Group	r*	Range (cm^2)	SEE* (cm^2)
			Mitral Stenosis			
Gorlin[1]	MVA by Gorlin formula vs direct autopsy or surgery	11	Mitral stenosis	0.89	0.5–1.5	0.15
Hakki[3]	MVA by original vs simplified Gorlin formula	40	Mitral stenosis	0.94	0.4–2.6	0.19
Libanoff[6]	T ½ at rest vs exercise	20	Mitral valve disease	0.98	20–340 ms	21 ms
Henry[7]	2-D echo vs direct measurement at surgery	20	MS pts. undergoing surgery	0.92	0.5–3.5	
Holen[8]	MVA by Doppler vs Gorlin	10	Mitral stenosis	0.98	0.6–3.4	0.18
Hatle[9]	T ½ vs Gorlin MVA	32	Mitral stenosis	−0.74	0.4–3.5	
Smith[10]	2-D echo vs Gorlin	37	MS alone	0.83	0.4–2.3	0.26
		35	Prior commissurotomy	0.58		0.28
	T ½ MVA vs Gorlin	(37)	MS alone	0.85		0.22
		(35)	Prior commissurotomy	0.90		0.14
Reid[19]	T ½ MVA vs Gorlin	12	Pre-CBV	0.80	0.6–3.6	0.4
	2-D echo vs Gorlin		Post-CBV	0.30		
			Pre- & post-CBV	0.80		
Come[20]	T ½ MVA vs Gorlin	37	Pre-CBV	0.51	0.6–1.3	
			Post-CBV	0.47	1.2–3.8	
	Gorlin vs Gorlin	23	Repeat cath	0.74	0.4–1.4	
Thomas[21]	Predicted vs actual	18	Pre-CBV	0.93–0.96		
	T ½		Post-CBV	0.52–0.66		
Abascal[22]	2-D echo vs Gorlin	17	Pre-CBV	0.81		
			Post-CBV	0.75		
			Pre- & post-CBV	0.88	0.5–3.0	
	T ½ MVA vs Gorlin	17	Pre-CBV	0.75		
			Immediately post	0.46		
			Follow-up	0.78	0.8–3.0	
Chen[23]	T ½ MVA vs Gorlin	18	Pre-CBV	0.81	0.4–1.2	0.11
			Immediately post-CBV	0.84	1.3–2.6	0.20
			24–48 hrs post-CBV	0.72	1.3–2.6	0.49
			Aortic Stenosis			
Hakki[3]	Simplified vs original Gorlin formula	60	Aortic stenosis	0.96	0.2–2.0	0.10
Skjaerpe[13]	Cont. eq. vs Gorlin	30	Aortic stenosis	0.89	0.4–2.4	0.12
Zoghbi[14]	Cont. eq. vs Gorlin	39	Aortic stenosis	0.95	0.4–2.0	0.15
Otto[15]	Cont. eq. vs Gorlin	103	Aortic stenosis	0.87	0.2–3.7	0.34
Tierstein[16]	Cont. eq. vs Gorlin	30	Aortic stenosis	0.88	0.3–1.6	0.17
Oh[17]	Cont. eq. vs Gorlin	100	Aortic stenosis	0.83	0.2–1.8	0.19
Danielson[18]	Cont. eq. vs Gorlin	100	Aortic stenosis	0.96	0.4–2.0	
Cannon[24]	Gorlin vs videotape of valve opening	42	Porcine valves in pulsatile flow model	0.87	0.6–2.5	0.28
	New formula vs actual orifice area	42	Porcine valves in pulsatile flow model	0.98	0.6–2.5	0.11
Segal[25]	Cont. eq. vs actual valve area		In vitro pulsatile flow with orifice plates	0.99	0.05–0.5	0.016
	Gorlin formula vs actual valve area			0.87		0.047
Cannon[26]	Gorlin vs known valve area	135	Prosthetic aortic valves 6 months after implantation	0.39	0.6–2.3	
Come[27]	Gorlin vs Gorlin	28	AS with repeat cath.	0.42	0.3–1.1	
	Cont. eq. vs Gorlin	40	Pre-BAV	0.71	0.2–1.1	
			Post-BAV	0.85	0.5–2.6	
Nishimura[28]	Cont. eq. vs Gorlin	55	Pre-BAV	0.72	0.2–0.9	0.10
			Post-BAV	0.61	0.5–1.3	0.17
Desnoyers[29]	Cont. eq. vs Gorlin	42	Pre-BAV	0.74	0.3–1.3	
Stoddard[30]	Cont. eq. vs Gorlin	41	Pre-BAV	0.84	0.2–0.8	0.08
			Post-BAV	0.87	0.3–1.2	0.10

*If not stated in the publication, statistics were calculated from the raw data provided in tables. A blank indicates that data for this calculation was not available.
AS = aortic stenosis; BAV = balloon aortic valvuloplasty; cath. = catheterization; CBV = catheter balloon valvuloplasty; Cont. eq. = continuity equation; echo = echocardiography; Gorlin = Gorlin formula valve area; MS = mitral stenosis; MVA = mitral valve area; 2-D = 2-dimensional; T ½ = pressure halftime.

graphic area prevalvuloplasty analysis. For both pre- and postvalvuloplasty gradients, the significant variables were cardiac output and heart rate at the time of echocardiography and at the time of catheterization.

Two-dimensional echocardiography and invasive mitral valve areas differed by ≤ 0.5 cm^2 in 96% and by <0.2 cm^2 in 81% of cases.

DISCUSSION

In this multicenter registry of patients undergoing aortic or mitral catheter balloon valvuloplasty, we examined factors that might account for discrepancies between invasive and noninvasive measures of stenosis severity.

Statistics: The overall correlations between invasive and noninvasive data are much poorer than those reported previously in studies designed specifically to validate the Doppler echocardiographic techniques (Table VI). However, both the invasive and noninvasive data in this registry were obtained as part of the routine clinical care in these patients at many different medical centers and may be more representative of the actual clinical use of these techniques than are previous studies of selected patients. In addition, statistical comparisons are difficult because selection of only those patients with severe stenosis results in a very narrow data range. The correlation coefficients in prior studies would be comparable to our findings if the data are restricted to those with severe disease.* Thus, despite the disappointing overall correlation coefficients, further analysis of this data is warranted.

Nonsimultaneous data collection: Given that the hemodynamic data were recorded immediately before and after the valvuloplasty, whereas the Doppler echocardiographic data were recorded up to 30 days before and 0 to 72 hours after the procedure, it is not surprising that there were spontaneous changes in loading conditions, as evidenced by the difference in heart rate and blood pressure between the 2 studies. The corresponding changes in flow rate would be expected to alter the transvalvular pressure gradient and could account for much of the discrepancy between the 2 methods of measuring transvalvular gradient, especially since several studies have demonstrated excellent correlation between invasive and noninvasive pressure gradients when recorded *simultaneously* in both human and animal studies.[12,36]

It is unlikely that significant changes in valve area due to disease progression occurred in the 30 days before the procedure.[37] However, in the period after valvuloplasty, rapid changes in valve area can occur due to elastic recoil of the aortic root in aortic stenosis,[38,39] and of the mitral apparatus in mitral stenosis. This factor may account for our observation that noninvasive valve areas are smaller than invasive valve areas after the procedure. In addition, valve area is not constant in an individual patient and can vary with loading conditions, heart rate, or volume flow rate.[40]

Transvalvular volume flow measurement: Another potential source of disagreement between the invasive and noninvasive techniques is the method used to calculate transvalvular volume flow. In the catheterization laboratory, forward cardiac output was used in the valve area calculation. In aortic stenosis patients with coexisting aortic insufficiency (88% of our population), and in mitral stenosis patients with coexisting mitral regurgitation (71% of our population), Fick or thermodilution cardiac output is not equal to volume flow across the stenotic valve, so that the calculated orifice area at catheterization will underestimate stenosis severity. In contrast, the Doppler method for aortic valve area measures transaortic volume flow just proximal to the stenotic valve,[41] the 2-dimensional echocardiographic mitral valve area does not rely on volume flow measurement,[9] and the halftime method is independent of transmitral volume flow rate.[8-10] This factor may account for our observation that the noninvasive valve area is larger than the invasively measured valve area before the procedure. The importance of this factor is supported by the influence of cardiac output and coexisting aortic regurgitation on the difference between catheterization and Doppler aortic valve areas, and by the effect of cardiac output on the correlations between invasive and noninvasive mitral valve areas. In addition, stroke volume may increase in the first 3 days after the procedure and result in greater aortic valve gradients by Doppler echo in the postprocedure time period.[42,43]

Technical expertise: As noted in previous studies, technical factors are important in the clinical use of these methods. There may have been substantial variability between medical centers in the degree of expertise with these techniques. Whereas the data do not allow distinction as to whether the invasive or noninvasive method is "at fault," the importance of careful attention to technical details with both approaches again deserves emphasis.

Potential observer bias: For both invasive and noninvasive data, the observers were aware of whether the data were recorded before or after the valvuloplasty procedure. Additional bias may be present for the invasive data in that the interventional cardiologist who performed the valvuloplasty typically analyzed the data and unintentionally may have found the procedure more beneficial than would an independent observer.

Inherent accuracy of measures of stenosis severity: Accuracy involves several factors including technical aspects of data collection for both invasive and noninvasive techniques, intra- and interobserver variability both in recording and in measuring the data, underlying assumptions in the formulas used, physiologic variability, and the reference standard itself. Because we compared the 2 techniques with each other, it is difficult to address this issue directly.

Whereas invasive measures of stenosis severity have been the clinical standard for the past 30 years, there are acknowledged limitations of this approach,[24,25,44,45] including dependence of valve area on cardiac output and variability of the "constant" in the Gorlin formula. A reasonable estimate is that an invasively determined valve area is accurate to only ±0.2 cm^2.[45]

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*For example, the r value of 0.87[15] with a range of aortic valve areas from 0.3 to 4.8 cm^2 decreases to $r = 0.70$ if only valve areas <1.5 cm^2 are included.

Similarly, the more recently introduced Doppler echocardiographic techniques have definite limitations both in data acquisition and measurement and in the underlying assumptions. Particularly in the patient after valvuloplasty, some of the assumptions may not be warranted, as has been demonstrated for the mitral half-time valve area and its dependence on left atrial and ventricular compliance.[21] Based on published intra- and interobserver variability data, the best possible accuracy of a Doppler aortic valve area is ±0.15 cm^2,[37] a half-time mitral valve area is about 0.30 cm^2, and a 2-dimensional echocardiographic mitral valve area 0.34 cm^2.[46]

Clinically, the inherent accuracy of techniques for assessing stenosis severity is not a problem, since our goal is to separate patients with severe stenosis from those with mild or moderate disease. However, in assessing the results of aortic valvuloplasty, the recorded changes in valve area are just at the limits of accuracy of both our measurement techniques. Although the group mean data show an unequivocal increase in valve area after the procedure with both techniques, interpretation of the changes in an individual patient is more difficult. The underlying accuracy of these techniques most likely is a major factor in apparent discrepancies when comparing absolute values of valve area in an individual patient.

Although the change in stenosis severity after the procedure as measured by the 2 methods is statistically different, both techniques show a hemodynamically similar increase in valve area and a decrease in pressure gradient. Thus, either technique provides a useful clinical assessment of the hemodynamic benefit of the procedure, and even if the 2 methods do not agree "closely," this probably is not of clinical relevance. The difference between the 2 methods for valve area was nearly always ≤ 0.5 cm^2, and was <0.2 cm^2 in most cases.

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APPENDIX: BALLOON VALVULOPLASTY REGISTRY

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Predictors of Exercise Benefit After Operative Relief of Left Ventricular Outflow Obstruction by the Myotomy-Myectomy Procedure in Hypertrophic Cardiomyopathy

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To determine predictors of exercise benefit in patients with hypertrophic cardiomyopathy after operative relief of left ventricular (LV) outflow tract obstruction, 30 patients underwent catheterization and exercise testing before and 6 months after operation, and hemodynamic measurements were obtained. The increase in maximal oxygen consumption (VO_2max) during treadmill exercise testing was chosen as an index of exercise benefit. Univariate analysis showed a significant positive correlation of operative change in VO_2max with preoperative LV end-diastolic and pulmonary arterial wedge pressures, operative change in exercise duration, and operative reductions in LV end-diastolic and pulmonary arterial wedge pressures and resting LV outflow tract gradient, and a significant negative correlation with preoperative VO_2max and percent predicted VO_2max. Multivariate analysis by stepwise linear regression of only significant univariate variables selected only preoperative percent predicted VO_2max, and operative reduction in LV end-diastolic pressure and resting LV outflow tract gradient as significant predictors of postoperative change in VO_2max. Stepwise regression analysis, applied only to preoperative exercise and catheterization hemodynamic variables, selected only preoperative percent predicted VO_2max and preoperative LV end-diastolic pressure as predictors of improvement in exercise capacity. Thus, patients with obstructive hypertrophic cardiomyopathy, after failing medical therapy, are most likely to demonstrate improvement in exercise capacity if preoperative exercise testing demonstrates limited exercise capacity and if surgery achieves reduction in elevated resting LV outflow tract gradients and LV filling pressures.

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Patients with hypertrophic cardiomyopathy manifest a wide variety of symptoms during effort, including dyspnea, chest pain and light-headedness.[1] After medical therapy is unsuccessful in controlling symptoms, operative relief of the obstruction by either removing muscle from the cephalad portion of the septum or replacing the mitral valve leaflets with prosthetic valves has been performed in a subset of these patients with left ventricular (LV) outflow tract obstruction.[2–12] Most, but not all, patients report a subjective improvement in symptoms after surgery.[2–12] However, these operative procedures are associated with an approximately 5% mortality,[5–6,8,10,12] and no study has been done to show if they prolong survival. To identify patients most likely to manifest improved exercise capacity after surgery, we measured hemodynamics and treadmill exercise capacity before and 6 months after operation in patients undergoing operation for relief of LV outflow tract obstruction.[13–15]

METHODS

This study was performed in conjunction with our standard hemodynamic assessment of the effects of LV septal myotomy-myectomy in patients with hypertrophic cardiomyopathy. This report includes data from 30 consecutive patients (17 men and 13 women aged 22 to 66 years [average 43]) severely limited by symptoms (New York Heart Association functional class III and IV) despite attempts at medical therapy with β blockers and calcium antagonists, who had large LV outflow tract gradients (>50 mm Hg under resting conditions or during isoproterenol infusion), and underwent identical preoperative and postoperative studies (approximately 6 months after operation). A 6-month postoperative follow-up was deemed an appropriate and optimal time for testing for improvement. All cardiac medications were discontinued for ≥5 drug half-lives before performance of noninvasive and invasive studies. The study protocol described below was approved by the Institute Review Board of the National Heart, Lung, and Blood Institute, and all patients gave informed consent.

Catheterization study: After an overnight fast and diazepam 10 mg orally, patients were taken to the catheterization laboratory usually at 8:00 A.M. Introducers were placed in the right femoral vein and artery for catheter access, followed by 5,000 U of heparin intravenously. A balloon-tipped thermodilution catheter was positioned in the pulmonary artery for measurements of pulmonary artery wedge pressure and cardiac output

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TABLE I Patient Characteristics

		Hemodynamic Data					Treadmill Exercise Data					
Pt.	Age (yr) & Gender	LVOT Gradient	Provokable Gradient	LVEDP	PAW	CI	Duration (min)	Max. HR	RPP	VO_2max	% Predicted VO_2max	AT
						Preoperative						
1	22M	62	136	14	10	4.5	5.6	144	24	21	46	1,350
2	23F	37	90	24	19	2.7	4.7	151	18	19	52	650
3	27M	90	—	16	17	3.0	9.6	157	17	22	44	1,000
4	29M	140	—	25	13	2.5	5.8	171	29	19	49	1,025
5	32M	5	80	14	10	3.5	7.0	160	25	26	63	1,050
6	32M	100	140	16	12	3.1	6.9	147	29	24	60	1,050
7	33M	100	135	18	11	2.2	10.8	176	27	21	55	1,100
8	34F	95	—	26	25	2.8	4.2	132	25	15	49	600
9	34F	85	150	28	40	—	7.2	141	23	21	58	1,400
10	35M	60	160	10	3	1.9	9.7	141	19	26	56	900
11	35F	125	—	34	24	2.5	2.7	142	18	13	38	900
12	35M	65	135	18	16	2.2	5.5	148	16	14	31	900
13	36F	50	80	16	12	2.4	3.3	186	32	14	58	800
14	44F	60	100	24	22	1.7	4.4	142	12	14	43	550
15	44F	110	—	34	31	2.6	3.6	152	22	15	45	600
16	44F	115	—	27	28	2.4	3.8	152	17	7	27	500
17	45M	92	—	18	12	1.9	6.1	169	24	18	66	1,475
18	46F	100	110	26	26	3.1	3.2	129	14	12	39	625
19	47M	75	115	15	14	2.7	5.9	160	22	18	73	850
20	48F	80	120	14	14	2.3	5.3	136	19	14	70	975
21	49M	0	145	12	10	2.8	3.0	126	19	15	58	1,000
22	50M	50	150	25	15	2.4	1.8	133	18	17	62	1,500
23	50M	115	—	32	26	2.3	1.9	121	20	13	52	1,300
24	51M	60	100	20	24	3.4	6.6	155	23	23	82	1,400
25	54M	140	—	20	19	2.4	7.5	120	20	18	52	850
26	59M	40	130	34	23	2.8	4.0	125	24	12	45	650
27	63F	100	125	20	16	2.9	4.5	128	15	16	61	850
28	64M	60	150	12	10	2.0	6.9	131	25	18	68	1,300
29	64F	155	—	22	14	2.9	1.9	137	25	13	67	900
30	66F	120	—	18	17	2.9	4.1	160	32	16	51	700
Mean		79	119	21	17	2.6	5.3	146	22	17	56	969
± SD		40	28	7	7	0.5	2.3	16	5	4	15	309

(average of ≥3 measurements). An end-hole pigtail catheter was positioned in the body of the left ventricle with attention to avoiding catheter entrapment.[16] LV and arterial pressures (referenced to the ascending aorta) were measured simultaneously in the resting state in all patients and during Valsalva maneuver, amyl nitrite inhalation, and isoproterenol infusion in 19 patients. The LV gradient was localized to the LV outflow tract during pullback of the catheter from the LV apex to the aorta in all cases. All patients subsequently underwent left ventriculography in which an angiographic pigtail catheter was used. During the preoperative study, all patients underwent selective coronary arteriography with use of multiple angulated views. All patients had completely normal epicardial coronary arteries as assessed by at least 1 cardiologist during formal review of the cineangiograms, and the consensus of staff cardiologists at a weekly conference.

Exercise study: All patients performed symptom-limited exercise on a treadmill with continuous electrocardiographic monitoring according to the Bruce protocol. One investigator monitored the patient throughout exercise; neither the investigator nor the patient could observe the timer on the exercise monitor. Arterial blood pressure was monitored continuously with an intraarterial catheter. Ventilation variables were measured with breath-by-breath analysis of expired gases (SensorMedics Horizons MMC 4400, Anaheim, California) and included the following parameters[17]: (1) maximal oxygen consumption (VO_2max) per kilogram during exercise (ml O_2/min/kg); (2) percent predicted VO_2max for a population of same age, gender, weight and height; and (3) ventilation anaerobic threshold, from visual inspection of the curves relating minute ventilation to oxygen consumption, and carbon dioxide release versus oxygen consumption and time. These determinations were averaged for each subject (ml O_2/min).

Operative treatment: All patients were candidates for surgical relief of outflow obstruction because of an LV outflow tract gradient of >50 mm Hg in the resting state (26 patients) or during isoproterenol infusion (4 patients). All 30 patients underwent septal myotomy-myectomy.

Statistics: Preoperative and postoperative patient characteristics are summarized as mean ± SD. Operative changes were computed as postoperative minus preoperative for the exercise variables, and preoperative minus postoperative for the hemodynamic variables. Preoperative and postoperative data were compared using the 2-tailed paired *t* test. For univariate analysis, simple linear regressions were performed adjusting for age and gender. Multivariate analysis was performed using stepwise linear regression with age and gender forced into the model. Regression model assumptions

TABLE I (continued)

	Hemodynamic Data					Treadmill Exercise Data					
Pt.	LVOT Gradient	Provokable Gradient	LVEDP	PAW	CI	Duration (min)	Max. HR	RPP	VO$_2$max	% Predicted VO$_2$max	AT
					Postoperative						
1	15	40	6	6	3.4	8.6	169	23	24	62	1,275
2	10	20	19	12	1.7	7.0	175	37	25	82	900
3	0	—	16	16	2.7	10.2	141	25	25	55	1,100
4	0	—	8	6	2.8	11.1	191	39	24	74	1,050
5	0	10	14	12	2.7	7.3	165	17	23	51	1,100
6	0	56	11	11	2.2	9.0	172	29	27	76	1,100
7	0	42	18	12	2.4	11.2	158	23	24	66	1,200
8	0	—	12	4	2.5	7.4	166	23	14	46	700
9	30	100	14	8	—	9.2	164	27	26	78	1,200
10	80	95	11	11	2.0	10.6	194	40	20	34	1,025
11	0	—	21	18	2.4	4.5	133	16	21	55	1,000
12	40	110	22	18	2.1	6.8	160	21	18	47	1,100
13	0	10	18	12	2.8	5.2	188	28	12	41	825
14	45	110	16	10	2.3	8.8	160	29	18	77	700
15	100	—	32	16	4.7	4.2	130	21	15	46	600
16	20	—	25	22	3.4	5.8	162	27	15	150	600
17	15	—	18	18	1.9	6.5	103	12	15	46	1,100
18	0	60	12	11	2.6	6.7	158	28	22	123	800
19	20	143	12	10	2.5	7.0	165	32	19	79	1,275
20	12	85	13	8	1.9	3.9	149	29	13	65	975
21	0	90	8	8	2.9	2.1	144	23	15	53	1,175
22	0	0	10	7	2.6	5.5	143	20	18	68	900
23	10	—	8	11	2.5	4.5	124	20	16	73	1,250
24	0	40	16	9	3.0	7.4	162	25	20	70	1,300
25	34	—	20	12	2.6	7.1	130	24	15	33	650
26	18	135	8	8	2.5	7.1	130	25	18	93	1,075
27	17	130	19	14	2.2	6.4	136	28	15	60	900
28	0	100	8	6	2.3	6.9	148	23	23	86	1,400
29	40	—	9	4	2.4	4.5	160	29	17	75	900
30	4	—	12	9	2.5	6.0	172	26	18	67	700
Mean	15	65	15	11	2.6	6.9	155	26	19	67	1,003
± SD	23	46	6	4	0.6	2.2	20	7	4	24	244

AT = anaerobic threshold (ml O$_2$/min); CI = cardiac index (liters/min/m^2); HR = heart rate; LVEDP = left ventricular end-diastolic pressure (mm Hg); LVOT = resting left ventricular outflow tract (mm Hg); Max. HR = maximal heart rate (beats/min); PAW = pulmonary arterial wedge pressure (mm Hg); RPP = rate-pressure product (beats/min × mm Hg × 10^3); VO$_2$max = maximal oxygen consumption (ml O$_2$/min/kg).

were checked through residual analysis (SAS statistical computer package 6.0, SAS Institute Inc., Cary, North Carolina).

RESULTS

Results of operation (Table I): HEMODYNAMIC DATA: Surgery decreased resting LV outflow tract gradient from 83 ± 38 to 17 ± 24 mm Hg (average reduction 66 ± 42, $p < 0.0001$), with 24 of 30 patients having ≥25 mm Hg reduction in resting LV outflow tract gradient. Similarly, 15 of 19 patients had a reduction of ≥25 mm Hg in their provokable LV outflow tract gradient (average reduction 51 ± 43, $p < 0.001$). LV filling pressures were also reduced after surgery from LV end-diastolic pressure of 21 ± 7 to 15 ± 6 mm Hg (average reduction 7 ± 8, $p < 0.001$), with 14 of 30 patients having a ≥5 mm Hg reduction in LV end-diastolic pressure. Similar results were found for pulmonary arterial wedge pressure (from 18 ± 8 to 11 ± 4 mm Hg, $p < 0.001$).

EXERCISE DATA: Surgery improved exercise duration from 5.3 ± 2.3 to 7 ± 2.2 minutes (average increase 1.7 ± 1.5, $p < 0.0001$), with 19 of 30 increasing their exercise duration by at least 1 minute. The maximal heart rate achieved at the end of the exercise was increased by 9 ± 21 beats/min ($p < 0.05$), whereas the maximal systolic arterial blood pressure achieved at the end of the exercise was increased by 17 ± 43 mm Hg ($p < 0.05$). The VO$_2$max increased after surgery from 17.1 ± 4.4 to 19.1 ± 4.3 ml O$_2$/min/kg (average increase 2 ± 3.9) ($p < 0.05$). The percent predicted VO$_2$max improved from 54 ± 12 to 68 ± 24% (average increase 13.6 ± 30) ($p < 0.05$). Anaerobic threshold increased from 958 ± 291 to 995 ± 224 (mean increase 38 ± 202 ml O$_2$/min, p = not significant).

UNIVARIATE ANALYSES (TABLE II): Change in VO$_2$max correlated with the initial LV filling pressure as measured by LV end-diastolic ($r = 0.51$) (Figure 1, top) and pulmonary arterial wedge ($r = 0.42$) pressures at rest as well as their reduction with operation ($r = 0.47$ [Figure 1, bottom]; $r = 0.34$) and the resting LV outflow tract gradient reduction produced by operation ($r = 0.35$) (Figure 2). Change in VO$_2$max correlated with the exercise duration change produced by operation ($r = 0.50$) as well as the initial VO$_2$max ($r = -0.48$) and its percent predicted value ($r = -0.60$) (Figure 3).

MULTIVARIATE ANALYSIS OF ALL VARIABLES: Multivariate analysis by stepwise linear regression of only significant univariate variables selected only the initial percent predicted VO$_2$max ($r^2 = 0.37$, $p < 0.005$), the reduction

TABLE II Univariate Analysis of Predictors of Change in VO_2max

Variables	No. of Pts.	p Value	r Value
Demographic			
Age	30	0.61	−0.09
Gender (M = 1; F = 0)	30	0.11	0.29
Hemodynamics:			
Preoperative			
LV outflow tract gradient	30	0.19	0.25
Provokable gradient	19	0.80	0.06
LV end-diastolic pressure	30	0.004	0.51
Pulmonary arterial wedge pressure	30	0.009	0.42
Cardiac index	29	0.77	0.05
Postoperative			
Δ resting gradient	30	0.06	0.35
Δ provokable gradient	19	0.63	−0.12
Δ LV end-diastolic pressure	30	0.009	0.47
Δ pulmonary arterial wedge pressure	30	0.06	0.34
Δ cardiac index	29	0.88	−0.02
Exercise			
Preoperative			
Duration	30	0.11	−0.30
Maximal HR	30	0.52	−0.12
HR × BP product	30	0.24	−0.22
VO_2max	30	0.007	−0.48
% predicted VO_2max	30	0.0005	−0.60
Anaerobic threshold	30	0.14	−0.27
Postoperative			
Δ duration	30	0.005	0.50
Δ maximal HR	30	0.47	0.13
Δ HR × BP product	30	0.29	0.20
Δ anaerobic threshold	30	0.07	0.33

BP = blood pressure; HR = heart rate; LV = left ventricular; VO_2max = maximal oxygen consumption (ml O_2/min/kg); Δ = change.

in LV end-diastolic pressure ($r^2 = 0.14$, $p < 0.01$) and the reduction in resting LV outflow tract gradient ($r^2 = 0.05$, $p = 0.10$) as predictors of the exercise benefit resulting from operation (total model $r^2 = 0.55$).

MULTIVARIATE ANALYSIS OF ONLY PREOPERATIVE VARIABLES: To establish a predictive equation for VO_2max change based only on preoperative clinically available variables, we selected only preoperative exercise and hemodynamic variables and again applied stepwise linear regression analysis forcing age and gender into the model. Only preoperative percent predicted VO_2max ($r^2 = 0.37$, $p < 0.0005$) and resting preoperative LV end-dia-

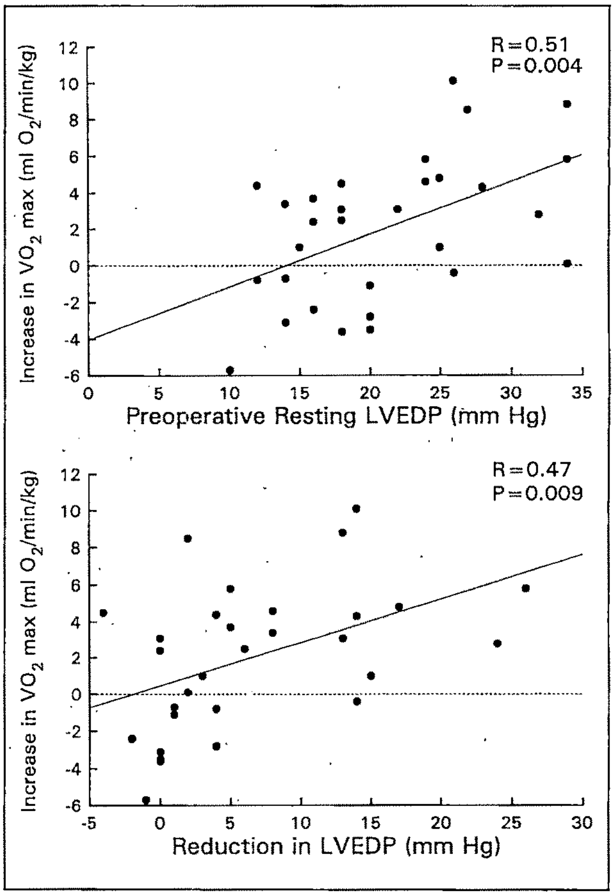

FIGURE 1. Plots of correlation of change in maximal oxygen consumption (VO_2max) after septal myotomy-myectomy with preoperative resting left ventricular end-diastolic pressure (LVEDP) *(top panel)* and operative change in LVEDP *(bottom panel)*.

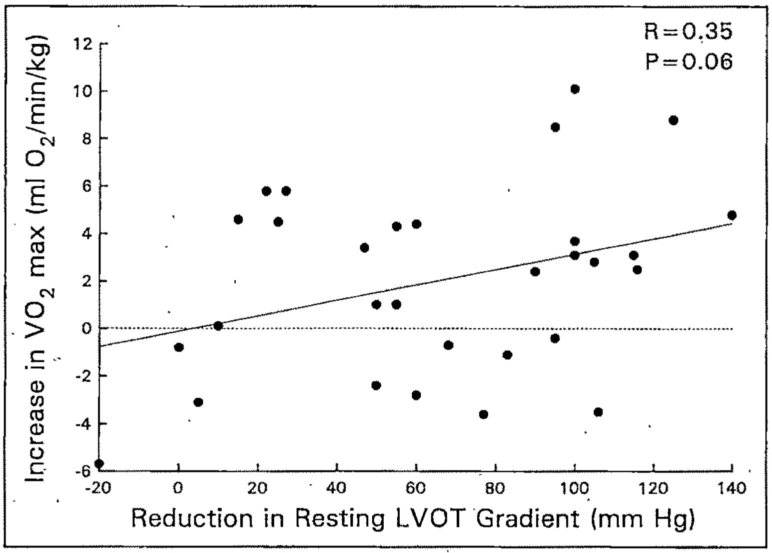

FIGURE 2. Plot of correlation of change in maximal oxygen consumption (VO_2max) after septal myotomy-myectomy with operative change in left ventricular outflow tract (LVOT) gradient.

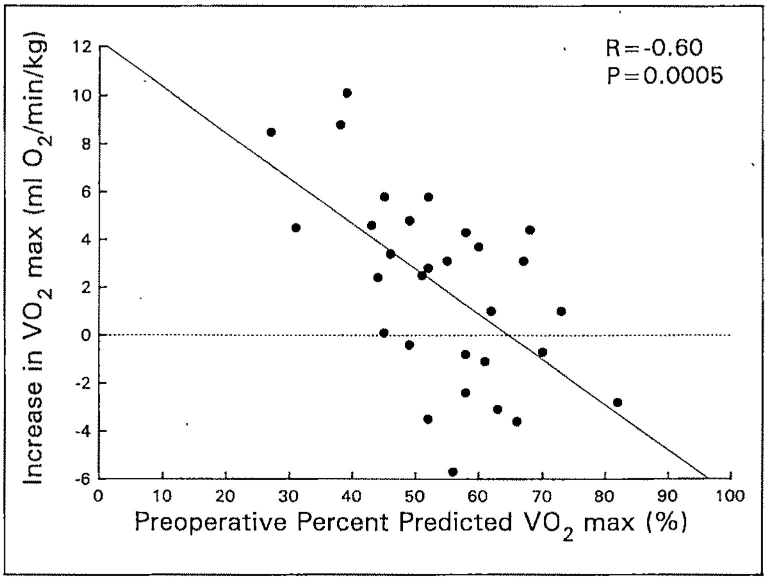

FIGURE 3. Plot of correlation of change in maximal oxygen consumption (VO$_2$max) after septal myotomy-myectomy with preoperative percent predicted VO$_2$max.

stolic pressure ($r^2 = 0.06$, $p = 0.11$) were selected as predictors of exercise benefit (total model $r^2 = 0.43$).

DISCUSSION

Previous studies have reported improvement in symptoms by operative relief of LV outflow tract obstruction in patients with hypertrophic cardiomyopathy, usually determined by functional class assessment.[4-12] To avoid potential biases of subjective assessment of symptom benefit, we chose to measure VO$_2$max as an objective marker of maximal exercise capacity.[13-15] The hemodynamic results with regard to reduction in LV outflow tract gradients and LV filling pressures in this series of patients are similar to previous series reported by our group and others.[1-12] Univariate analyses showed that several variables correlated well with objective improvement in exercise capacity. Among them were elevated LV filling pressures and their change by operation, as well as the operative change in resting LV outflow tract gradient. With regard to the exercise parameters, only postoperative change in exercise duration correlated with a postoperative change in VO$_2$max.

To build a model that best predicts operative change in VO$_2$max, stepwise linear regression analysis was used. Analyzing all variables, including preoperative and postoperative hemodynamics and exercise parameters, we found 3 variables to be good joint predictors of exercise benefit, combining to predict 55% of the variation in operative change in VO$_2$max. In order of their contribution to r^2, these were: (1) greater preoperative effort limitation as assessed by low preoperative percent predicted VO$_2$max; (2) reduction in LV filling pressure as assessed by a reduction in LV end-diastolic pressure, and (3) a reduction in resting LV outflow tract gradient. The model was not changed when adjusted for age and gender, which themselves were not significant predictors.

Finally, to find a model that could be applied prospectively to patients selected to undergo surgery for relief of symptoms, we applied stepwise linear regression analysis only to the variables available to us before operation, so that only age, gender and preoperative exercise and hemodynamic data were included in the analysis. Our results show that only greater preoperative effort limitation as assessed by low preoperative percent predicted VO$_2$max and high preoperative filling pressures as assessed by LV end-diastolic pressure were predictors of improvement in exercise capacity. The model explained 43% of the variation in operative change in VO$_2$max. Resting and provokable LV outflow tract gradient did not turn out to be important predictors because of the lack of variability in these 2 parameters in our study population (a significant LV outflow tract gradient was taken as the criteria for performing operation).

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Doppler Echocardiographic Assessment of the Pressure Gradient During Bicycle Ergometry in Hypertrophic Cardiomyopathy

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To assess the behavior of the subvalvular pressure gradient under physical exercise, 13 patients with obstructive hypertrophic cardiomyopathy were examined during upright bicycle ergometry by means of Doppler echocardiography. Additionally, right-sided cardiac catheterization was performed within 7 days. In 10 patients adequate Doppler tracings could be obtained during exercise. The Doppler-derived systolic pressure gradient increased from 75 ± 24 to 140 ± 42 mm Hg ($p < 0.0005$). This was associated with an increase in the duration of the systolic mitral-septal contact from 59 ± 21 to 136 ± 28 ms ($p < 0.0005$). Correlation between the pressure gradient and the duration of mitral-septal contact at rest and during exercise was good ($r = 0.86$), whereas correlation between the resting and exercise pressure gradient ($r = 0.34$) did not reach statistical significance. The increase in stroke volume during exercise, from 90 ± 18 to 95 ± 24 ml, was significant ($p < 0.05$) but minimal. Therefore, only a moderate increase in systolic flow, from 205 ± 54 to 268 ± 78 ml/s ($p < 0.0005$), was observed. Outflow tract resistance, defined as the ratio of the pressure gradient to systolic flow, increased from 0.38 ± 0.11 to 0.57 ± 0.24 mm Hg · s/ml ($p < 0.01$). Thus, in a selected group of patients with hypertrophic cardiomyopathy a substantial increase in the maximal pressure gradient during upright bicycle ergometry was demonstrated in most patients. Exercise Doppler echocardiography may be valuable to assess the hemodynamic significance of obstruction in individual patients in a physiologic setting and has a potential to monitor the effect of therapeutic interventions.

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The presence of a systolic pressure gradient in patients with hypertrophic cardiomyopathy (HC) is generally attributed to obstruction to left ventricular outflow.[1–8] This has been the rational basis for surgical abolition of the gradient and normalization of intraventricular pressures either by septal myotomy-myectomy[9–11] or by mitral valve replacement.[12] Nevertheless, even the subgroup with the obstructive form of the disease is quite heterogeneous and covers a broad spectrum of patients, including those in whom diastolic abnormalities may prevail over obstruction.[2,13–15] Therefore, assessment of the functional significance of obstruction may be critical in selecting patients who could benefit from surgery. To date, this has been performed by testing the effects of provocative measures (induction of ectopic beats, inhalation of amyl nitrite, infusion of nitroglycerin and isoproterenol, performance of the Valsalva maneuver) on the pressure gradient.[16–19] Whether these interventions truly reflect the hemodynamic situation of a physiologic stress test is unknown. The present study was conducted to examine the behavior of the subvalvular obstruction during physical exercise by means of Doppler echocardiography in a selected group of patients with obstructive HC.

METHODS

Patients: Thirteen patients with HC, who were referred to our institutions for consideration of myotomy-myectomy, were examined. Diagnosis was confirmed by the echocardiographic demonstration of a nondilated, hypertrophied left ventricle in the absence of any other cardiac or systemic disease capable of producing left ventricular hypertrophy.[5] The patients had a subvalvular pressure gradient at rest of ≥50 mm Hg, assessed by cardiac catheterization or Doppler echocardiography, or both. For inclusion into the study the following criteria had to be met: technically satisfactory M-mode and 2-dimensional echocardiograms at rest and high-quality left ventricular outflow tract signals at rest and during exercise. In 10 patients, satisfactory Doppler tracings were obtained during physical exercise. The clinical and echocardiographic features of these patients, who were finally included into the study, are listed in Table I.

Echocardiography: A Toshiba SSH-160 A or a Hewlett Packard 1000 Sonos electronic sector scanner with a 2.5 MHz transducer as well as a 2.0 MHz nonimaging transducer were used to examine the patients in an upright position on a bicycle ergometer with the chest bent slightly forward. M-mode tracings of the mitral valve were recorded from the parasternal window.

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The left ventricular outflow tract was visualized from an apical transducer position. The wall filter and gain settings were adjusted to optimally display the left ventricular outflow tract velocity signals. Special care was taken to distinguish the flow velocity signals of outflow tract obstruction from those of mitral regurgitation by color flow and continuous-wave Doppler. The patients then performed bicycle ergometry at work loads of 2 minutes 50 W and 2 minutes 75 W with the transducer position on the apex of the heart. During end-exercise, after the best possible signal of left ventricular outflow tract velocity had been recorded, the transducer was repositioned to the parasternal window in order to obtain M-mode tracings of the systolic anterior motion of the anterior mitral leaflet.

The following parameters were determined at rest and during exercise: heart rate (beats per minute), duration of the mitral-septal contact (ms), the instantaneous pressure gradient, using the modified Bernoulli equation[20]: $\Delta P = 4 V^2$, where ΔP is the instantaneous pressure gradient (mm Hg) and V the measured maximal flow velocity (m/s). The Doppler ultrasound beam direction was assumed to be close to the direction of blood flow and therefore no angle correction was used in calculating the pressure gradient.

Right-sided cardiac catheterization: Within 7 days, Swan-Ganz catheterization was performed at rest and during exercise at work loads of 2 minutes 50 W and 2 minutes 75 W in the supine position. Cardiac output (ml/min) was determined by the thermodilution technique; cycle length and QT time(s) were obtained from the electrocardiogram, and mean pulmonary artery pressure (mm Hg) was continuously monitored.

The following parameters were calculated for rest and exercise conditions: stroke volume = cardiac output/60 · cycle length (ml), systolic flow = cardiac output/60 · cycle length/QT time (ml/s), and outflow tract resistance = pressure gradient/systolic flow (mm Hg · s/ml) according to Poiseuille's law.

Data analysis: All quantitative results of the study were expressed as mean value ± standard deviation. Differences between rest and exercise values were tested by Student's paired 2-sample *t* test. Correlation between different parameters was assessed by linear regression analysis using the least-squares method.

TABLE I Clinical and Echocardiographic Features of 10 Patients with Hypertrophic Cardiomyopathy

Pt.	Age (yr) & Sex	NYHA Class (I–IV)	Verapamil Daily Doses (mg/day)	LVEDD (mm)	LVESD (mm)	VS (mm)	LV Wall (mm)
1	21 F	II	240	41	15	25	12
2	33 M	II	480	40	21	19	10
3	39 M	II	240	49	25	20	11
4	39 M	III	—	46	23	24	12
5	44 F	III	—	40	23	25	15
6	44 M	I	—	48	22	29	13
7	47 M	I	480	47	22	30	13
8	48 M	II	—	49	30	23	13
9	50 M	III	—	45	20	21	12
10	71 F	III	320	44	21	24	12

LVEDD = left ventricular end-diastolic dimension; LVESD = left ventricular end-systolic dimension; LV Wall = left ventricular wall thickness; NYHA = New York Heart Association class of symptoms; VS = ventricular septum thickness.

RESULTS

Symptoms: Five patients experienced dyspnea during exercise, 3 patients angina pectoris in addition to dyspnea, and 2 patients were asymptomatic at the end of the study.

Outflow tract velocity signal: The maximal systolic outflow tract velocities ranged from 3.5 to 5.6 (mean 4.28 ± 0.67) m/s at rest and 5 to 7.5 (mean 5.87 ± 0.85) m/s during exercise (37% increase, p <0.0005). Figure 1 demonstrates continuous-wave Doppler ultra-

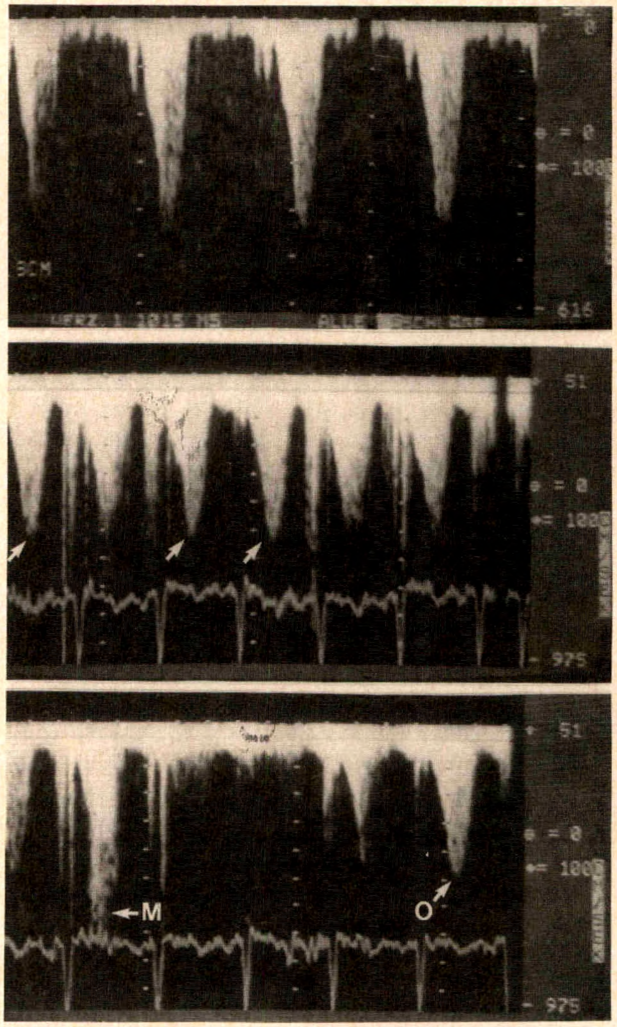

FIGURE 1. Spectral recording of the continuous-wave Doppler ultrasound signals from the left ventricular outflow tract at rest and during exercise in a patient with hypertrophic cardiomyopathy and a subvalvular pressure gradient. At rest *(top)*, maximal systolic flow velocity is 4.1 to 4.2 m/s, corresponding to a calculated pressure gradient of 69 mm Hg. During exercise *(middle)*, flow velocity increases to 5.1 m/s, corresponding to a Doppler-derived gradient of 104 mm Hg. Note that the characteristic shape of a velocity signal in a dynamic outflow tract obstruction — a gradual increase, a midsystolic acceleration and a late systolic peak — is preserved during exercise *(arrows)*. *Bottom*, also during exercise, the outflow tract signal (O) can easily be distinguished from a signal that was "contaminated" by a superimposed high-velocity signal of mitral regurgitation (M).

sound signals from the left ventricular outflow tract at rest and during exercise in a patient with obstructive HC. The flow velocity increased from 4.1 to 4.2 m/s at rest to 5.1 m/s during exercise, corresponding to an increase in the calculated pressure gradient from 69 to 104 mm Hg. The characteristic shape of a velocity signal in a dynamic outflow tract obstruction — a gradual increase, a midsystolic acceleration and a late systolic peak — was preserved during exercise. It could easily be distinguished from a signal that was "contaminated" by a superimposed high-velocity signal of mitral regurgitation.

Mitral valve echogram: A mitral M-mode echocardiogram could also be obtained during exercise in 6 of the 10 patients (Figure 2): At rest the systolic anterior motion of the anterior mitral leaflet did not result in septal contact. During exercise mitral-septal contact developed early in systole and was prolonged. Left ventricular internal dimensions at the level of the mitral valve decreased: At end-diastole from 4.2 ± 0.4 to 4.0 ± 0.5, at end-systole from 2.3 ± 0.4 to 1.9 ± 0.2 ($p < 0.03$). The duration of the mitral-septal contact ranged from 25 to 83 (mean 59 ± 21) ms at rest and 117 to 188 (mean 136 ± 28) ms during exercise (see Figure 3).

Hemodynamics: Figure 3 illustrates the hemodynamic changes during exercise, assessed by echocardiography and right-sided cardiac catheterization. There was an increase in heart rate from 70 ± 14 to 114 ± 15 beats/min during exercise Doppler echocardiography. No patient showed a deviation of >3 beats/min in heart rate at corresponding work loads during exercise echocardiography and the right heart catheterization study.

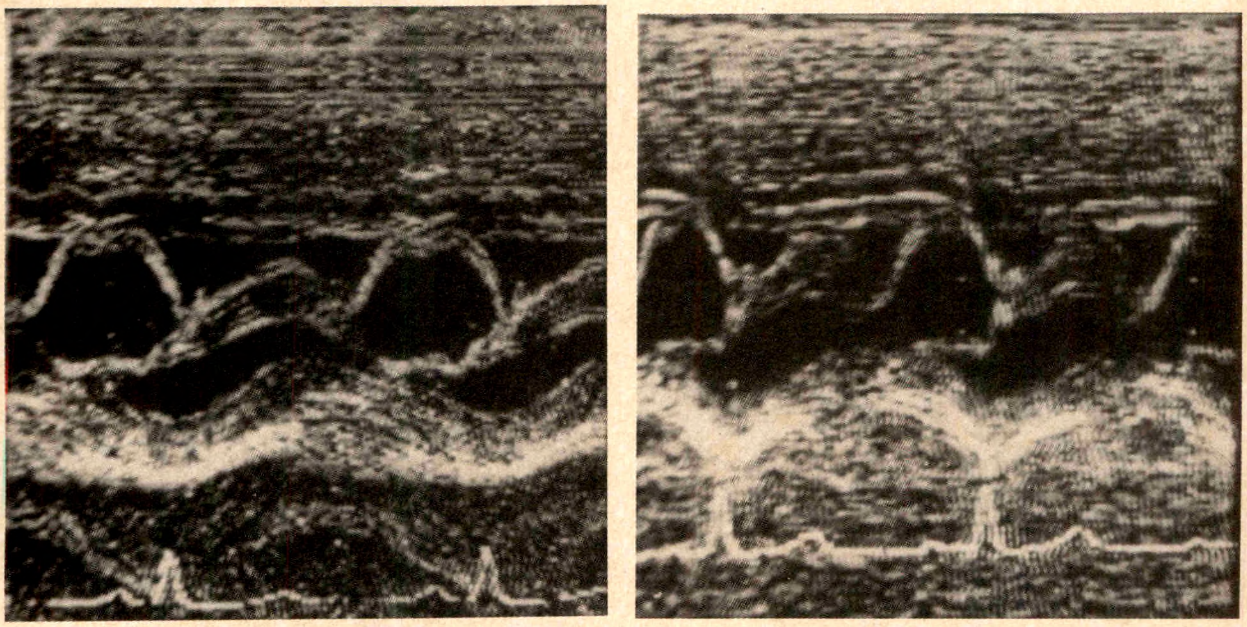

FIGURE 2. Systolic anterior motion of the anterior mitral leaflet at rest and during end-exercise. At rest *(left)* time from onset of the systolic anterior motion to its maximum is long, the plateau period short and mitral-septal contact is not reached (in the image plane). During exercise *(right)* mitral-septal contact develops early in systole and is prolonged. Left ventricular internal dimensions decrease during exercise.

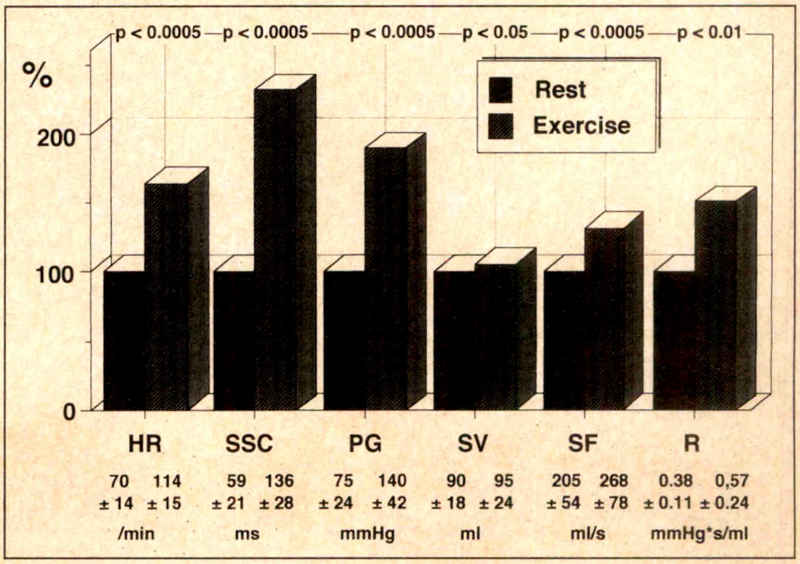

FIGURE 3. Hemodynamics at rest and during exercise assessed by echocardiography and right-sided cardiac catheterization in 10 patients with hypertrophic cardiomyopathy and a significant subvalvular pressure gradient. HR = heart rate (beats/min); PG = Doppler-derived subvalvular pressure gradient; R = outflow tract resistance; SF = systolic flow; SSC = duration of the systolic mitral-septal contact; SV = stroke volume.

The pressure gradient increased from 75 ± 24 to 140 ± 42 mm Hg (87% increase on average with a range from 13 to 250%, $p < 0.0005$). This was associated with an increase in the duration of mitral-septal contact from 59 ± 21 to 136 ± 28 ms ($p < 0.0005$) in 6 patients, in whom satisfactory M-mode echocardiographic tracings of the mitral motion could also be obtained during exercise. Correlation between the pressure gradient and the duration of mitral-septal contact was good ($r = 0.86$, SEE = 24 mm Hg, $p < 0.05$), whereas correlation between the resting and exercise pressure gradient was poor and did not reach statistical significance ($r = 0.34$, SEE = 46 mm Hg, $p > 0.25$) (Figures 4 and 5). The increase in stroke volume during exercise from 90 ± 18 to 95 ± 24 ml was significant ($p < 0.05$) but minimal. Therefore, there was only a moderate increase in systolic flow, from 205 ± 54 to 268 ± 78 ml/s (31% increase, $p < 0.0005$). The outflow tract resistance increased from 0.38 ± 0.11 to 0.57 ± 0.24 mm Hg · s/ml (50% increase, $p < 0.01$).

DISCUSSION

We studied a selected group of patients with obstructive HC at rest and during exercise using Doppler echocardiography to determine systolic pressure gradients from left ventricular outflow tract velocities according to the modified Bernoulli equation.[21,22] Color flow Doppler was helpful to avoid a contamination of the outflow tract signal by a superimposed signal of a mitral regurgitant jet. However, careful evaluation of the continuous-wave Doppler signal alone[23] provided all necessary information. The characteristic flow velocity pattern of subvalvular obstruction, which accurately reflects the timing of the pressure differences across the outflow tract throughout systole,[21] consists of a gradual increase with a midsystolic acceleration and a comparatively sharp peak in late systole. In contrast, the mitral regurgitant signal starts earlier and shows a rapid increase in velocity, corresponding to the rapid increase in the left ventricular–left atrial pressure difference in early systole (Figure 1).

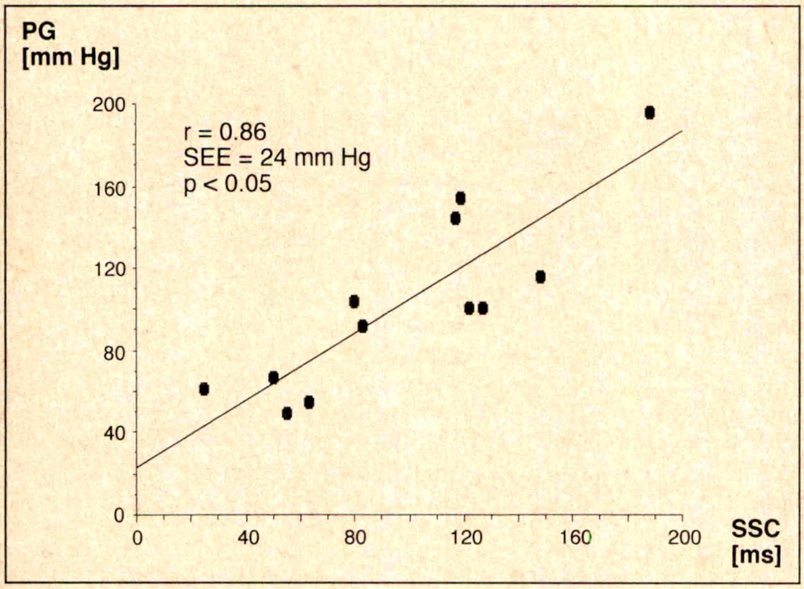

FIGURE 4. Quantitative relation between the duration of the systolic mitral-septal contact (SSC) and the pressure gradient (PG) at rest and during exercise in 6 patients with hypertrophic cardiomyopathy.

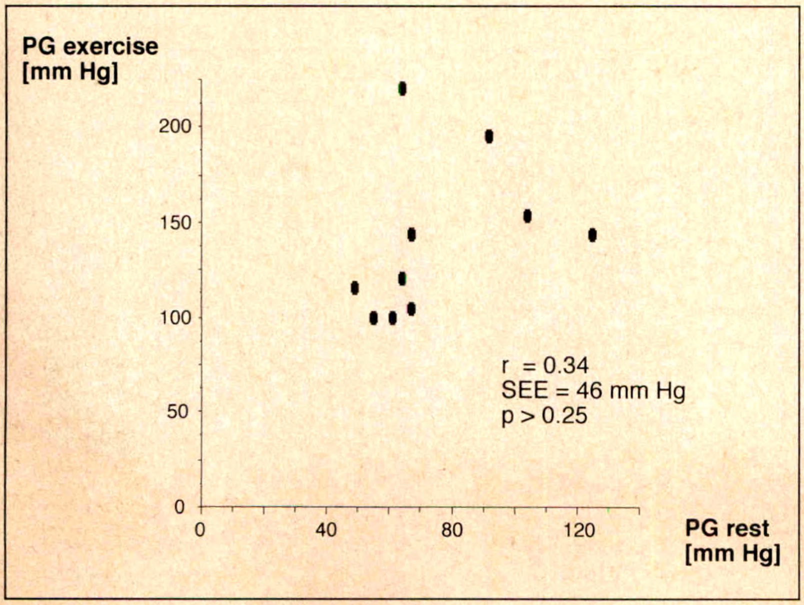

FIGURE 5. Lack of correlation between Doppler-derived pressure gradients at rest (PG rest) and during exercise (PG exercise) in 10 patients with hypertrophic cardiomyopathy.

In the patient group studied in this report, a nearly 90% increase in the pressure gradient was found. The quantitative relation between the duration of the mitral-septal contact and the pressure gradient, previously demonstrated using pharmacologic interventions,[24] was preserved during exercise (Figures 3 and 5). This is compatible with a causal relation between mitral-septal contact and a dynamic obstruction to left ventricular outflow. Right-sided cardiac catheterization during exercise was performed at comparable work loads to rule out that the observed increase in the pressure gradient during exercise was merely due to an increase in systolic flow in the presence of an unchanged outflow tract resistance. We found only a minimal increase in stroke volume, characteristic for patients with HC.[25] Therefore, the estimated systolic flow showed only a moderate increase (due to a shortened systolic ejection time during exercise) insufficient to account for the substantial increase in the pressure gradient. Consequently, the calculated outflow tract resistance increased by 50%.

The fact that right-sided cardiac catheterization was not performed simultaneously with the Doppler study and in the supine position, unlike the Doppler stress test, has obviously introduced an error of measurement. Because of the magnitude of the exercise-induced changes in the pressure gradient, it is unlikely that this has significantly affected the results of the study.

The response of the pressure gradient to physical exercise could not be predicted by the pressure gradient at rest (Figure 5). One patient with a systolic pressure gradient of 125 mm Hg at rest had only an increase to 144 mm Hg during exercise (Figure 6). Pulmonary capillary wedge pressure was 20 mm Hg at rest and 40 mm Hg during exercise. The calculated outflow tract resistance was 0.54 mm Hg · s/ml at rest and 0.50 mm Hg · s/ml during exercise, suggesting no substantial change in outflow tract resistance (or rather a decrease). A possible mechanism for this phenomenon has been proposed by Grbic[26] and Klues[27] and their co-workers: The substantial increase in left ventricular end-diastolic pressure that occurs during exercise in many patients with HC may reflect augmented left ventricular filling (in the presence of reduced compliance) due to an increase in venous return. This should lead to an increase in left ventricular cavity dimensions and therefore limit or even prevent an increase in the systolic pressure gradient. Interestingly, when reexamined 2 weeks later with unchanged medication, the aforementioned patient had a spontaneous resting gradient of 64 mm Hg that increased to 100 mm Hg during and 130 mm Hg after exercise.

Our findings are in accordance with the first systematic investigations by Harrison et al,[28] assessing pressure gradients in patients with HC after cardiac catheterization during supine bicycle ergometry. They reported an average increase of the peak systolic pressure gradient from 46 mm Hg at rest to 79 mm Hg during and to 84 mm Hg after exercise, with a decrease in the calculated outflow tract area from 1.31 to 0.87 cm^2 during exercise, which also represents an increase in outflow tract resistance by 50%. They found an increase in the gradient in 6 patients (in 1 patient from 11 to 100 mm Hg), in 3 of the others it remained unchanged, and in 1 it declined.[29] The further increase of the gradient shortly after the cessation of exercise, which was observed in the majority of patients, is assumed to be due to a further decrease in the outflow tract area by the combination of a sudden reduction in venous return to the heart, coupled with a persistently low peripheral resistance and a continuation of the sympathetic stimuli to the heart. In the present study, we also observed an additional increase in the pressure gradient after the cessation of exercise in some of the patients. However, this question was not systematically addressed, because the patients were soon brought into supine position in order to diminish the exercise-induced gradient.

In contrast to the studies by Braunwald et al, 2 other studies[26,27] could not demonstrate an increase in the systolic pressure gradient during exercise, but only in the immediate postexercise period, as mentioned. The dif-

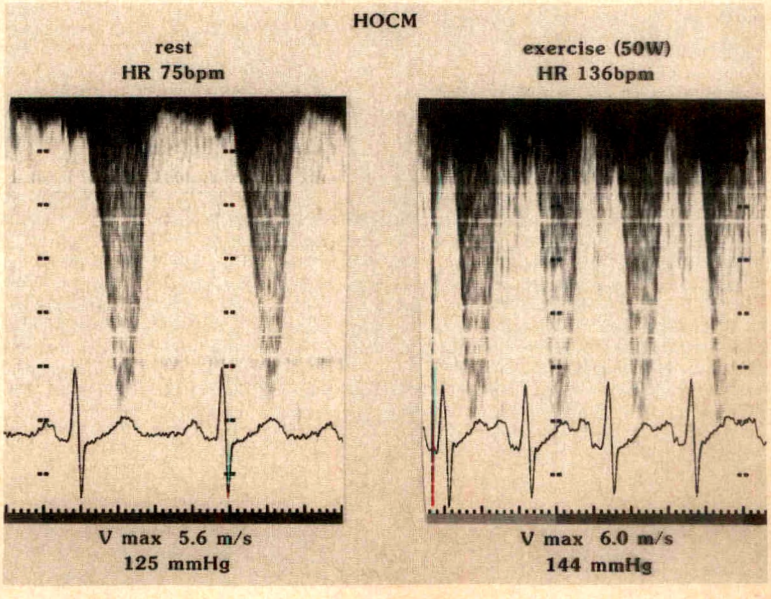

FIGURE 6. Outflow tract velocity signals at rest and during exercise in a patient with hypertrophic cardiomyopathy (HOCM) with a remarkable pressure gradient. The outflow tract velocity increases from 5.6 m/s at rest to 6.0 m/s during exercise (at 50 as well as at 75 W), which corresponds to a mild increase in the calculated pressure gradient from 125 to 144 mm Hg. Calculated outflow tract resistance is 0.54 mm Hg · s/ml at rest and 0.50 mm Hg · s/ml during exercise, suggesting that the mild increase in pressure gradient is not related to an increase in outflow tract obstruction, but in systolic flow. HR = heart rate; V max = maximal velocity.

ferences between these investigations, including ours, can partially be explained by different patient selection, which has to be expected, when a relatively small number of patients with a heterogeneous disease is examined. In addition, the present study differs from the other studies in 3 important aspects: First, assessment of the systolic pressure gradient during bicycle ergometry was performed in the upright position, which reflects physical exercise during everyday activity better than supine bicycle ergometry. The pressure gradient has been shown to be higher in the upright than in the supine position.[29] Because an increase in the size of a poorly compliant left ventricle during exercise is particularly unlikely to occur in the upright position, the gradient may also increase to a greater extent during upright physical activity: In fact, in patients whose M-mode data were available during exercise, internal dimensions decreased on average. An increase in end-diastolic pressure and filling is more apt to limit an increase in the pressure gradient in the supine position (especially with elevated legs). Second, in contrast to the invasive studies, we did not assess the peak-to-peak systolic pressure gradient, just the Doppler-derived maximal instantaneous pressure gradient, which is usually higher and may also show a higher increase. Third, Doppler echocardiographic assessment of the systolic pressure gradient in patients with HC provides the maximal gradient at the vena contracta, which determines the load on the proximal chamber. Levine et al[30] demonstrated that this is of great importance in the presence of the special geometry of obstruction in this disease: The streamlined subvalvular stenoses allow for pressure recovery just as in flow meters, which are inserted into pipelines. Pressure recovery is increasing with the rate of flow, so that it may even become more important during exercise. In case of invasive measurement, underestimation of the true maximal pressure gradient will occur if the distal catheter is not exactly placed at the vena contracta, but only 1 cm away from it.

Further work is necessary to determine the clinical and prognostic implications of pressure gradients during exercise, especially in patients without any resting obstruction.

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MISCELLANEOUS

Impairment of Left Ventricular Diastolic Function in Systemic Lupus Erythematosus

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Left ventricular (LV) diastolic performance was evaluated with pulsed-wave Doppler echocardiography in a cross-sectional population of patients with systemic lupus erythematosus (SLE) in search of subclinical myocardial involvement. Such involvement is reported to occur infrequently, despite pathohistologic evidence of myocarditis in up to 70% of patients with SLE. Thirty-five consecutive patients with SLE were evaluated, 14 with active and 21 with inactive disease, and were compared with 30 age-matched healthy control subjects. Twenty-six patients were restudied at 7 months. All had normal LV systolic function, normal pericardial and valvular structures, and no significant valvular regurgitation on Doppler echocardiography. In SLE patients with active disease, indexes of LV diastolic function differed significantly from the inactive group and from control subjects, with marked prolongation of isovolumic relaxation time (104 ± 18 vs 74 ± 13 ms, $p = 0.0001$), as well as reduced peak early diastolic filling velocity (E) (0.69 ± 0.19 vs 0.83 ± 0.17 ms, $p = 0.01$), reduced ratio of early to late diastolic flow velocity (E/A) (1.15 ± 0.53 vs 1.47 ± 0.35, $p = 0.02$), and prolonged mitral pressure halftime (74 ± 14 vs 65 ± 8 ms $p = 0.01$). Similar significant differences were found between the active and inactive SLE patient groups. SLE patients with inactive disease differed from control subjects in only mild prolongation of mitral pressure halftime. Abnormal prolongation of isovolumic relaxation (>100 ms) was found to be the most useful marker of diastolic impairment, being present in 64% of SLE patients with active disease and in 14% of patients with inactive disease. LV diastolic function did not change appreciably in the 26 patients restudied at 7 months, although there was a trend for improvement in the 5 active patients who became inactive at follow-up. It is concluded that impaired LV diastolic function is common and persistent in patients with SLE, especially in those with active disease. This most likely represents myocardial involvement in the lupus process. Further long-term studies are required to determine the clinical and prognostic implications of these findings.

(Am J Cardiol 1992;69:1629–1634)

Clinical cardiac manifestations of systemic lupus erythematosus (SLE) are usually limited to pericardial and valvular involvement. Despite the 40 to 70% prevalence rate of myocarditis in autopsy series of patients with SLE, the reported incidence of clinically apparent myocardial dysfunction in these patients is 5 to 10% over the course of the disease.[1-3] This discrepancy between the clinical and pathologic findings suggests sublinical involvement that may be detected by a more sensitive diagnostic tool. Impairment of left ventricular (LV) diastolic function, which often precedes systolic dysfunction, has been shown to be a sensitive marker for myocardial involvement in various cardiac disease states.[4] LV diastolic function in lupus patients has not been adequately investigated, and its course over time has not been studied previously. We have recently evaluated several patients with SLE who developed cardiogenic pulmonary edema during an acute exacerbation of their underlying disease. Doppler echocardiography revealed impairment of LV diastolic function as the only detectable abnormality. We assessed LV diastolic function using Doppler echocardiography in a cohort of consecutive SLE patients with no clinically apparent heart disease or echocardiographic evidence of impaired LV systolic function, valvular or pericardial abnormalities. The study aims were threefold: (1) determine the prevalence of isolated diastolic dysfunction in this population; (2) correlate the severity of diastolic dysfunction with clinical parameters of disease activity; and (3) determine whether the impairment in diastolic function varies temporally with SLE disease activity.

METHODS

Patient: Thirty-five consecutive patients (10 inpatients and 25 outpatients; 6 men and 29 women) who consented to participate in this study were recruited from the SLE Clinic and Rheumatology ward at The Wellesley Hospital, a regional referral center for rheumatic diseases at the University of Toronto. All patients met the revised diagnostic criteria of the American Rheumatism Association for the classification of SLE.[5] Their mean age was 41 years (range 22 to 84) and mean duration of SLE since diagnosis was 7.1 years

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(range 0.1 to 23). All patients included in the study met the following criteria: (1) no clinical evidence of cardiac disease [in particular no history of angina, myocardial infarction, previous cardiac surgery or cardiac abnormalities on physical examination]; (2) normal 12-lead electrocardiogram; (3) normal LV wall thickness, dimensions and systolic function on 2-dimensional echocardiography; and (4) normal pericardial and valvular structures, and no significant (more than mild) valvular regurgitation on Doppler echocardiography.

The study patients were categorized as having active disease or inactive disease according to the lupus activity criterion count of ≥2 or <2, respectively.[6] At the baseline study, 14 of the 35 patients were active and 21 were inactive. Twenty-six of the initial 35 patients were restudied at 7 months (Figure 1). Of the 21 inactive patients studied at baseline, 16 were restudied and all remained inactive. Of the 14 active patients at baseline, 10 were restudied: 5 remained active and 5 became inactive. Of the 9 patients who were not restudied, 4 died (3 in the active group), 3 could not be restudied for logistic reasons, and 2 were lost to follow-up. Thirty age-matched healthy subjects (mean age 40 years, range 25 to 60) with normal blood pressure, electrocardiogram, exercise test (if ≥40 years) and 2-dimensional echocardiogram served as normal control subjects.

Echocardiographic assessment of left ventricular diastolic function: M-mode, 2-dimensional and Doppler echocardiography were performed from the standard parasternal and apical views in the resting state, and in the supine or left lateral position. The standard M-mode measurements of LV wall thickness and internal dimensions were obtained from the parasternal long-axis view as recommended by the American Society of Echocardiography.[7]

LV diastolic function was assessed by pulsed Doppler echocardiography using the advanced technology laboratories Ultramark 8 (ATL-8) ultrasound system. This method of assessing LV filling is well established and has been validated against contrast and radionuclide angiography.[8-10] The variables measured included isovolumic relaxation time, defined as the time between aortic valve closure and mitral valve opening; peak early filling velocity (E); peak late filling velocity (A); the E/A ratio — a measure of the relative blood volume filling the left ventricle in early versus late diastole; and mitral pressure halftime — a measure of the deceleration rate of early diastolic flow. Transmitral flow was analyzed from the apical view, with a sample volume at the mitral leaflet tips level so as to obtain the highest E point velocity as well as the mitral opening and closure sounds. Isovolumic relaxation time was measured with sample volume at the LV outflow tract — closer to the aortic valve, so as to record both aortic closure and mitral opening sounds. Each parameter was measured at end-expiration and averaged over ≥5 consecutive analyzable beats. All measurements were obtained by a single observer unaware of the clinical status of the patients. The inter and intraobserver variability of these measurements, previously evaluated in this laboratory, are 6 and 4%, respectively.[11]

Statistical analysis: Results are expressed as mean ± 1 standard deviation, unless otherwise specified. Two-tailed unpaired Student's *t* test was used to compare SLE patients with the control group, and to compare SLE patients with active versus inactive disease. Paired

TABLE I Left Ventricular Diastolic Filling Parameters in Normal Subjects and in Patients with SLE at Baseline

	No. of Pts.	HR (beats/min)	IVRT (ms)	E (m/s)	A (m/s)	E/A	PHT (ms)
Normal subjects	30	66 ± 11	74 ± 13	0.83 ± 0.17	0.59 ± 0.13	1.47 ± 0.35	65 ± 8
SLE	35	73 ± 13*	89 ± 21†	0.74 ± 0.19*	0.55 ± 0.19	1.47 ± 0.57	72 ± 11†
SLE-ID	21	75 ± 10*	80 ± 17	0.77 ± 0.19	0.48 ± 0.11	1.65 ± 0.52	71 ± 9*
SLE-AD	14	70 ± 17	104 ± 18†	0.69 ± 0.19*	0.65 ± 0.25	1.15 ± 0.53*	74 ± 14*

*$p < 0.05$; †$p < 0.005$ compared with values in normal subjects.
Values are expressed as mean ± 1 SD.
A = peak late filling velocity; E/A = ratio of E to A; E = peak early filling velocity; HR = heart rate; IVRT = isovolumic relaxation time; PHT = mitral pressure halftime; SLE = systemic lupus erythematosus; SLE-AD = active disease; SLE-ID = inactive disease.

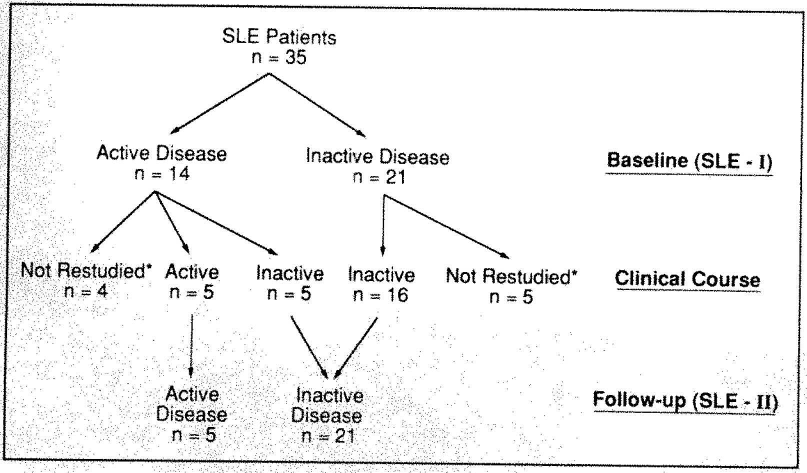

FIGURE 1. Flow diagram of the 35 patients with systemic lupus erythematosus (SLE) participating in the study at baseline (SLE-I) and at 7-month follow-up (SLE-II). *See text for details.

Student's *t* test was used for comparing the baseline findings with those at follow-up in the 26 patients restudied. Statistical significance was assumed at $p < 0.05$.

RESULTS

Patient characteristics: Of the 35 patients studied at baseline, 14 were active and 21 were inactive. Four patients gave a history of systemic hypertension, but were normotensive and receiving no antihypertensive therapy when evaluated. At the time of this study all 35 patients were normotensive (BP ≤140/90 mm Hg), with systolic and diastolic pressures of 116 ± 12 and 75 ± 10 mm Hg, respectively. Seventeen of the 35 patients were taking systemic steroid therapy (prednisone) at a dose of 12 ± 10 mg for a mean of 89 months (range 7 to 280). The distribution of patients receiving systemic steroids as well as those with history of hypertension was similar

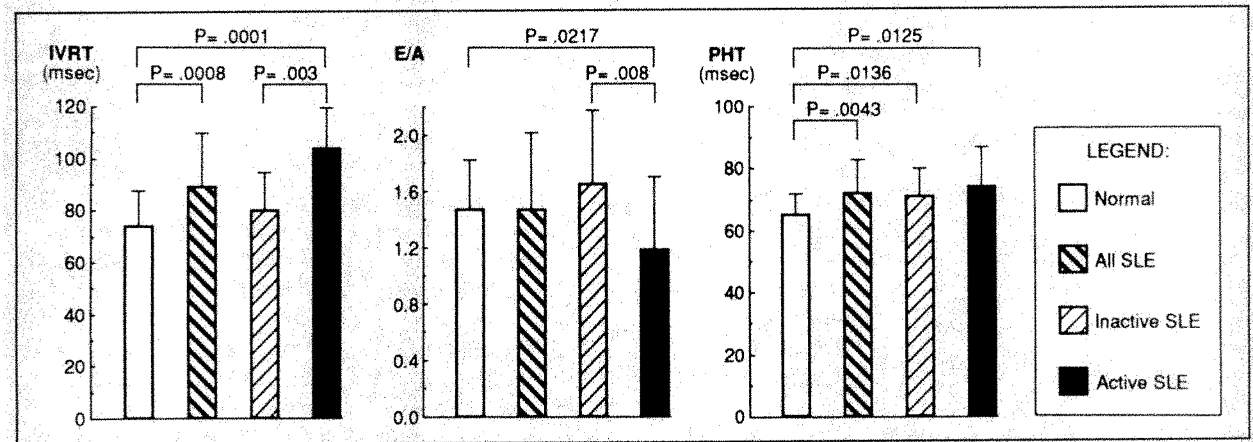

FIGURE 2. Bar graph comparison of left ventricular filling parameters (mean ± SD) in patients with systemic lupus erythematosus (SLE) and in control subjects at baseline. E/A = ratio of peak early (E) to late (A) transmitral diastolic flow velocities; IVRT = isovolumic relaxation time; PHT = mitral pressure halftime.

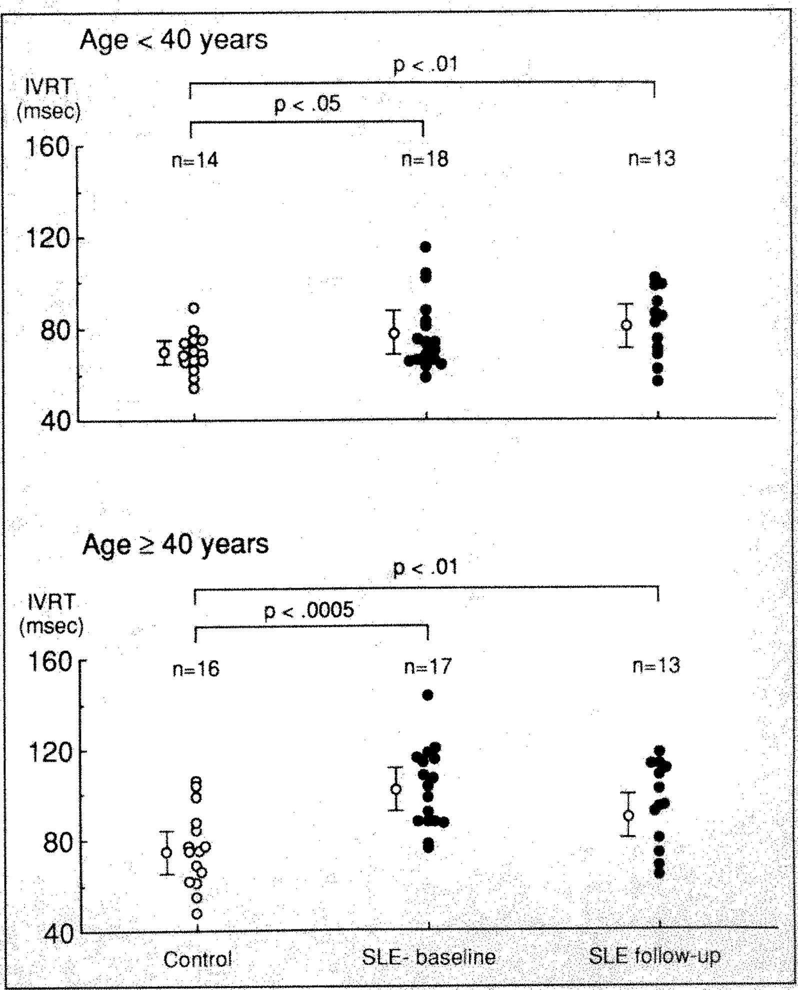

FIGURE 3. Scattergram of isovolumic relaxation times (IVRT), presented according to younger (<40 years) and older (≥40 years) age groups of control subjects and patients with systemic lupus erythematosus (SLE) at baseline and at 7-month follow-up. Impairment of diastolic performance with prolongation of IVRT was consistently found in the patients with SLE, irrespective of age, at baseline and at follow-up.

in both groups. Other anti-inflammatory drugs, azathioprine and chloroquine, were also similarly distributed between the 2 groups. LV dimensions, wall thickness and systolic function were normal and similar in both groups.

Left ventricular diastolic function: Results of the baseline study are summarized in Table I and in Figure 2. When compared with the normal group, the 35 patients with SLE had impaired diastolic function with abnormally prolonged isovolumic relaxation time (89 ± 21 vs 74 ± 13 ms, $p = 0.0008$), lower E velocity (0.74 ± 0.19 vs 0.83 ± 0.17 m/s, $p = 0.04$), and prolonged mitral pressure halftime (72 ± 11 vs 65 ± 8 m/s, $p = 0.004$). When grouped according to disease activity, the 14 patients with active disease had the most profound impairment of diastolic function, which differed significantly from those with inactive disease and from control subjects. On further analysis according to age, this impairment in diastolic performance (as expressed by prolonged isovolumic relaxation time) was consistently found in both the younger (<40 years) and older (≥40 years) patient groups (Figure 3).

TABLE II Prevalence of Abnormal Diastolic Parameters in SLE Patients with Active and Inactive Disease at Baseline

	No. of Pts.	IVRT (>100)	E (<0.49)	A (>0.85)	E/A (<0.77)	PHT (>0.81)
Active SLE	14	64%	84%	57%	57%	7%
Inactive SLE	21	14%	65%	28%	17%	0%

The numbers in parentheses indicate mean ± 2 SD of the control subjects.
Abbreviations as in Table I.

Table II and Figure 4 summarize the prevalence of abnormal diastolic parameters in the active and inactive groups in the baseline study. The upper and lower limits of normal were taken as the mean ± 2 standard deviations of these variables in the normal group. Prolongation of isovolumic relaxation time to >100 ms was found to be the most useful marker for disease activity, present in 9 of 14 of the patients (64%) with active disease, and in only 3 of 21 of those (14%) with inactive disease. Abnormalities in the other variables were also more frequent in patients with active disease.

The baseline and follow-up diastolic parameters in the 26 patients who were restudied after 7 months (SLE-2) are summarized in Table III. As a whole, diastolic function for this group remained impaired over the follow-up period. However, subgroup analysis according to disease activity at baseline and at follow-up revealed a trend for improvement in isovolumic relaxation time, from 110 ± 26 to 93 ± 16 ms ($p = 0.058$) in the 5 patients who were initially active and subsequently became inactive at follow-up (Figure 5). The isovolumic relaxation time remained stable (81 ± 18 vs 83 ± 18 ms) in the 16 patients who were inactive throughout.

DISCUSSION

In the present study, patients with SLE without overt cardiac manifestations were found to have disease-

TABLE III Left Ventricular Diastolic Filling Parameters in Normal Subjects, and in Patients with SLE at Baseline and at Seven-Month Follow-Up

	No. of Pts.	HR (beats/min)	IVRT (ms)	E (m/s)	A (m/s)	E/A	PHT (ms)
Normal	30	66 ± 11	74 ± 13	0.83 ± 0.17	0.59 ± 0.15	1.47 ± 0.35	65 ± 8
SLE-1	26	73 ± 13*	89 ± 22†	0.74 ± 0.19*	0.55 ± 0.20	1.47 ± 0.55	72 ± 8*
SLE-2	26	72 ± 12*	88 ± 18†	0.75 ± 0.16*	0.57 ± 0.20	1.41 ± 0.40	61 ± 12

*$p < 0.05$; †$p < 0.005$ compared with values in normal subjects.
SLE-1 = baseline study; SLE-2 = study at 7-month follow-up; other abbreviations as in Table I.

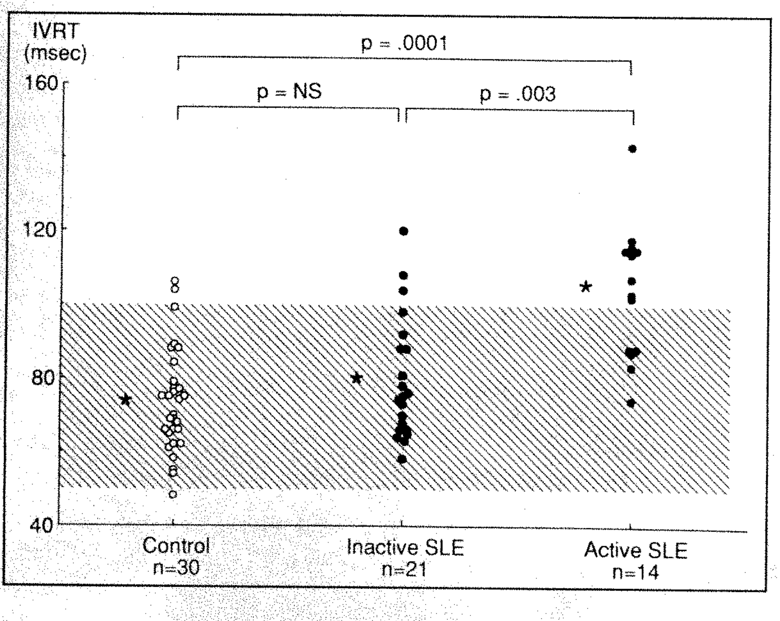

FIGURE 4. Scattergram of isovolumic relaxation times (IVRT) of the control group, and of patients with active and inactive systemic lupus erythematosus (SLE). IVRT in the group with active disease was significantly higher than in those with inactive disease ($p = 0.003$) and in control subjects ($p = 0.0001$). IVRT in patients with inactive disease did not differ from that in control subjects. *Shaded* area indicates the normal range as defined by mean ± 2 SD of the normal control subjects. NS = not significant; *mean value of IVRT in each group.

related impairment of LV relaxation compared with age-matched control subjects. Moreover, patients with active disease had more frequent and more pronounced impairment of LV relaxation than those without. This impairment of diastolic performance was not accompanied by any impairment of LV systolic function, valvular or pericardial abnormalities, or with any clinical cardiac manifestations. This impairment of diastolic performance persisted over the 7 months of follow-up, with a trend toward improvement in association with resolution of SLE disease activity.

These observations are in agreement and substantially add to previously reported invasive and noninvasive studies of myocardial involvement in patients with SLE.[12-17] Importantly, of the different variables measured in this study, the isovolumic relaxation time was found to best correlate with disease activity, being abnormally prolonged in 64% of patients with active disease compared with only 14% of those with inactive disease. The abnormal LV filling pattern seen in our patients is an early manifestation of myocardial dysfunction, similar to that previously reported in other cardiac disease states including hypertension,[18] coronary artery disease,[19] hypertrophic cardiomyopathy,[20] and inflammatory diseases such as scleroderma[21] and ankylosing spondylitis.[22]

In this study, our aim was to determine the prevalence of myocardial involvement in the lupus process, as manifested by impaired diastolic performance, in a population of SLE patients with no other complications known to effect LV diastolic filling pattern. Thus, none of the patients studied had clinical evidence of coronary artery disease, arrhythmias, hypertension, LV hypertrophy or impairment of LV systolic function. None had evidence of valvular or pericardial disease. These complications, which are not infrequent in the lupus population, are known to influence the LV filling pattern and may already indicate myocardial involvement. To control for the influence of age on these parameters,[23] patients with SLE were age-matched with healthy subjects. Furthermore, subgroup analysis according to age revealed persistent differences in diastolic function indicating that those differences are indeed independent of age. The patients with SLE as a group had a higher heart rate compared with control subjects (73 ± 13 vs 66 ± 11). This was not considered a significant factor because the difference was small, and the patients with active disease who had the greatest abnormality in diastolic function had a heart rate similar to control subjects. Additionally, isovolumic relaxation time — the parameter showing the most profound impairment — is the one least effected by changes in heart rate.[11]

The pathophysiologic basis for this impairment in LV diastolic function is unclear, and the lack of pathologic correlates in this study makes any hypothesis only speculative. However, the higher prevalence of impaired diastolic function in patients with active disease, the trend for improvement with resolution of disease activity, the frequent cardiac immunopathologic findings[24,25] and the high prevalence of lupus myocarditis in pathologic reports (40 to 70%) are all concordant and suggest a relation to an active inflammatory state involving the myocardium. The role of corticosteroids in either the development or treatment of impaired diastolic function in SLE is not known. Autopsy findings implicate corticosteroids with increased epicardial and myocardial fat deposition in patients with SLE.[26] We could not demonstrate a correlation of dose or duration of steroid therapy with the presence of diastolic dysfunction in this group of patients with SLE.

We conclude that impaired LV diastolic function is common in SLE in the absence of systolic abnormalities or any other clinical or echocardiographic evidence of cardiac involvement. This is more frequent and more pronounced in patients with active SLE. We believe this to be an early and otherwise subclinical manifestation of SLE-induced myocarditis and lupus cardiomyopathy. Further long-term studies are required to determine whether the diastolic abnormalities observed in this study have clinically significant prognostic implications.

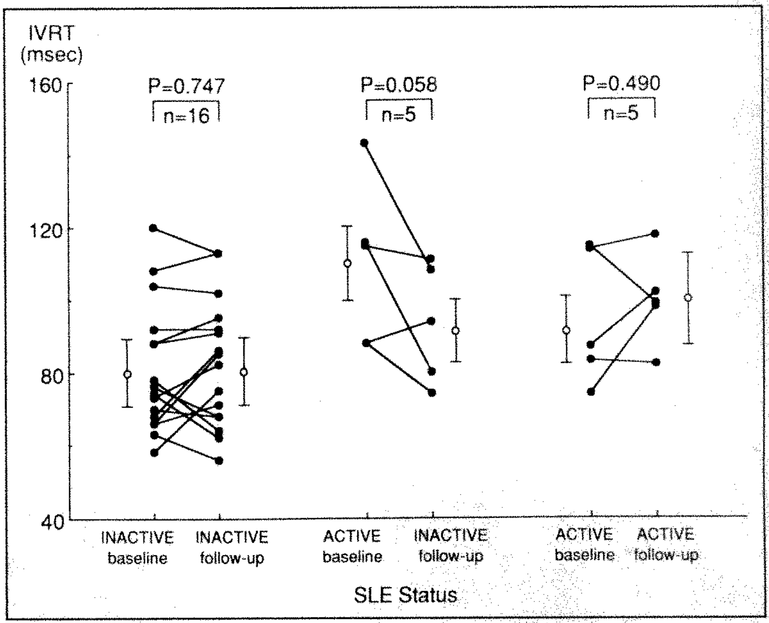

FIGURE 5. Changes in isovolumic relaxation times (IVRT) in the 26 patients with systemic lupus erythematosus (SLE) studied at baseline and at follow-up according to the disease activity. IVRT did not change significantly in the 16 patients who remained inactive, or in the 5 patients who remained active during the study. There was a trend for improvement in IVRT in the 5 initially active patients who became inactive at follow-up (p = 0.058). ***Open circles and bars*** **= mean ± 1 SD in each group.**

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Observations of Coronary Flow Augmentation and Balloon Function During Intraaortic Balloon Counterpulsation Using Transesophageal Echocardiography

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The intraaortic balloon pump has been shown to decrease myocardial oxygen demand by afterload reduction, while increasing myocardial oxygen supply by diastolic augmentation of coronary blood flow. This diastolic augmentation of coronary flow has been demonstrated experimentally with invasive methods. Noninvasively, transesophageal echocardiography has demonstrated efficacy in enabling visualization of the proximal left coronary artery and in recording coronary blood flow velocity. To assess the potential of this technique in demonstrating quantitatively the increase in coronary flow during counterpulsation, 6 patients were studied during intermittent balloon pumping. Peak diastolic coronary blood flow velocity increased by a mean of 117% (range 62 to 287) during balloon inflation ($p = 0.002$). Furthermore, coronary flow velocity integral increased by a mean of 87% (range 43 to 176; $p = 0.003$). Problems associated with intraaortic balloon pumping were discovered by transesophageal echocardiography in 4 patients (incorrect balloon placement, damage to the aortic wall [2 patients], and premature balloon deflation time). Transesophageal echocardiography can be used in evaluating intraaortic balloon positioning within the aorta and in monitoring coronary artery flow augmentation during counterpulsation. This relatively noninvasive technique adds another dimension to the evaluation of balloon function and may help in optimizing the benefits of counterpulsation.

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The physiologic benefits of intraaortic balloon counterpulsation include decreasing myocardial oxygen demand by afterload reduction, and increasing myocardial oxygen supply by diastolic augmentation of coronary blood flow.[1,2] Quantification of coronary artery blood flow during counterpulsation has been performed using invasive methods.[3,4] In some reports, augmentation of coronary blood flow of 40 to 50% was documented.[3,5] However, these methods are impractical in the clinical setting. Advances in transesophageal Doppler echocardiography enable us to detect proximal coronary artery blood flow when combined with 2-dimensional echocardiography.[6–11] In the present study, this technique was used to quantitate coronary flow augmentation during counterpulsation. Our observations suggest the potential of clinical applications for transesophageal echocardiography in monitoring placement and function of intraaortic balloon devices.

METHODS

We studied 6 patients (3 men and 3 women, aged 52 to 68 years) who needed intraaortic balloon pumping. Patient 1 needed the assist device for hypotension after mitral valve replacement. Patient 2 had balloon placement for unstable angina while awaiting surgery. Patient 3 was in shock after myocardial infarction. Patient 4 had hemodynamic collapse after mitral valve replacement, and 5 and 6 were in shock after bypass surgery. Three patients were studied intraoperatively. Indications for performing transesophageal echocardiography included: routine intraoperative monitoring of left ventricular function (patients 1, 2 and 6), exclusion of papillary muscle rupture or ventricular septal defect when transthoracic echocardiography was inconclusive (3 and 5), and investigation of possible prosthetic valve dysfunction (4).

Intraaortic balloon placement was accomplished percutaneously through the femoral artery, using methods previously described.[12,13] Balloon inflation was set at the dicrotic notch, and deflation began at midisovolumetric systole. The balloon displacement volume was 40 ml, whereas the assist ratio was set at 1:2 intermittently to allow comparison of coronary flow velocity during augmentation with that of an immediately preceding nonaugmented beat.

Transesophageal echocardiography: Transesophageal echocardiography was performed using a Hewlett-Packard Sonos 500 echocardiographic system (Andover, Massachusetts) and a 5 MHz transesophageal transducer. The descending thoracic aorta and aortic

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arch were examined. During imaging, the landmark for detection of the left coronary artery was the short-axis view of the aortic valve. High-resolution images of the proximal coronary arteries were obtained with anteflexion of the transducer. Color flow Doppler helped to locate the optimal scanning plane for visualization of coronary arteries. The pulsed Doppler sample volume was positioned within the coronary lumen in an area that minimized the angle between the incident Doppler beam and the direction of coronary flow. The sample volume was within the left anterior descending artery in 4 cases and within the left main in 2. Doppler recordings of multiple pairs of augmented and nonaugmented beats were obtained during 2:1 counterpulsation. The flow velocity time integral was calculated from the spectral display using a Cardiologic Analysis System (Sony Medical Electronics Company, Hackensack, New Jersey). The average peak flow velocity and flow velocity integral were calculated for 5 pairs of augmented and nonaugmented beats during 2:1 counterpulsation.

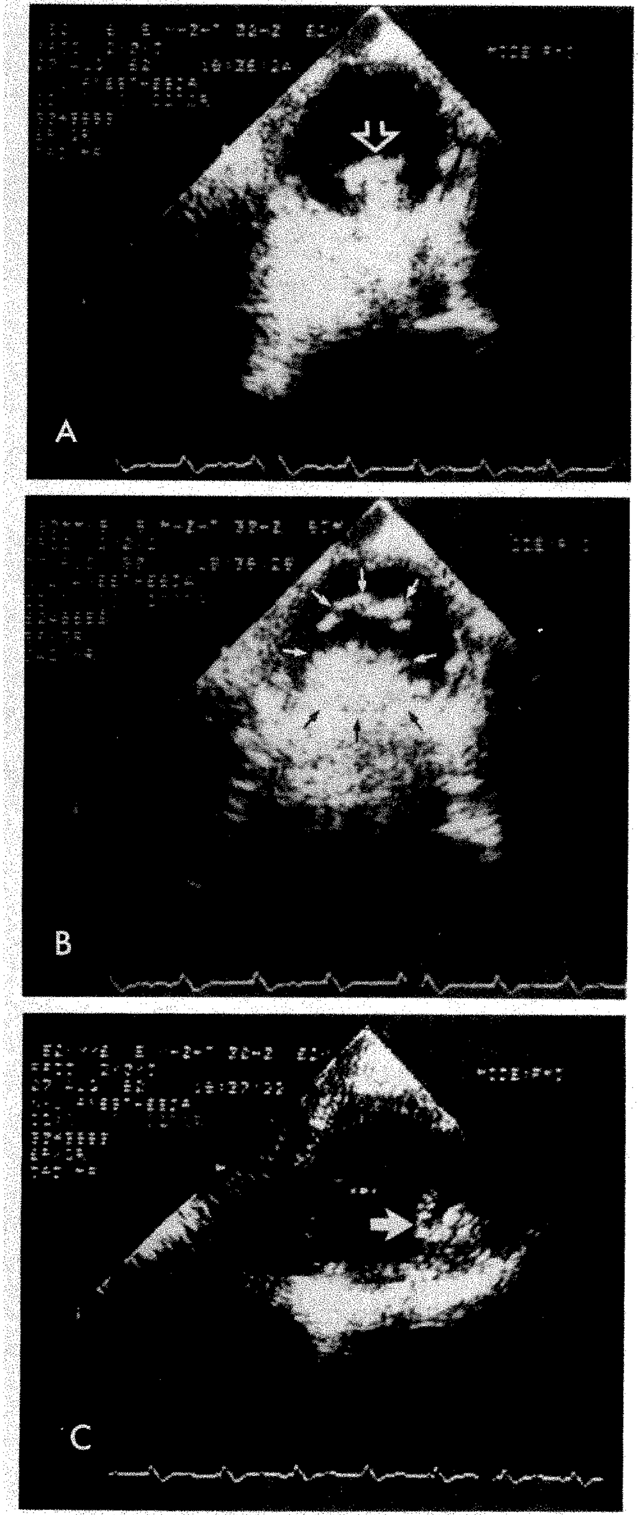


FIGURE 1. Transesophageal transverse image of descending thoracic aorta. *A*, deflated intraaortic balloon is seen within lumen *(open arrow)*. *B*, inflated intraaortic balloon *(arrows)* occludes most of aortic lumen. *C*, disrupted mobile plaque *(arrow)* is seen hanging from aortic luminal surface in area of balloon inflation.

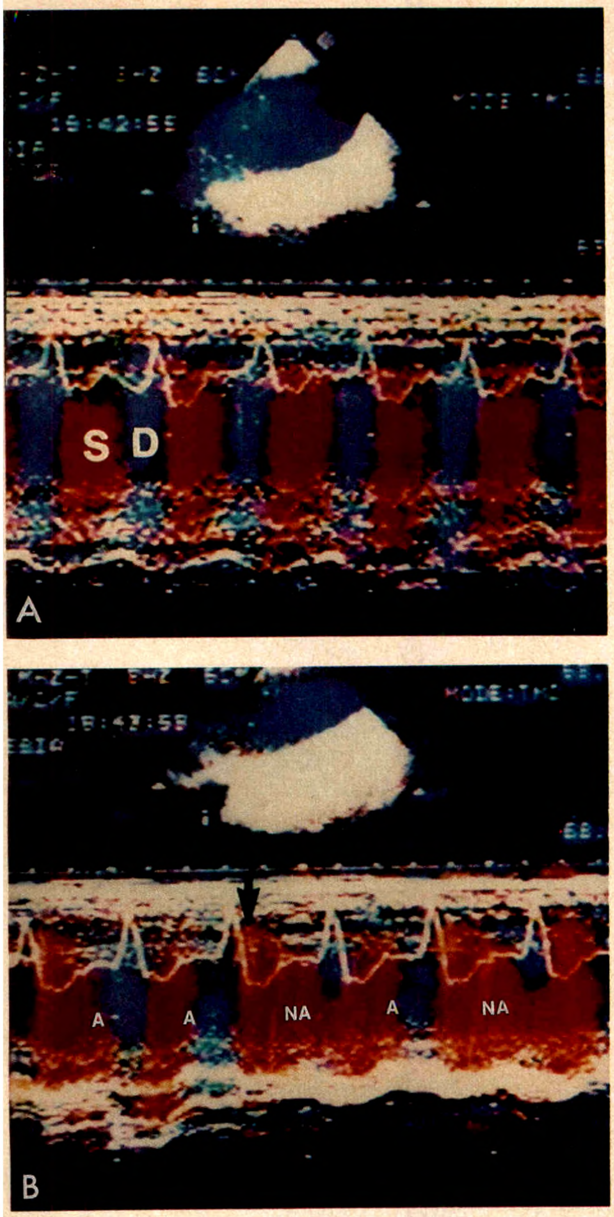
Statistical analysis: A 2-tailed Student's *t* test was used to compare the continuous variables of flow velocity and flow velocity integral at baseline with those of the augmented state. A p value ≤ 0.05 was considered significant.

RESULTS

Evaluation of intraaortic balloon placement and function: The balloon was visualized in the proximal segment of the descending thoracic aorta in each patient (Figure 1A). Visualization of the balloon in the distal transverse aorta prompted withdrawal of the device to past the point of origin of the left subclavian artery in 1 patient. Near total occlusivity of the aortic diameter by the intraaortic balloon was seen in all patients during diastolic inflation (Figure 1B). Gross damage to the aortic intimal surface was noted in 2 patients. In the area of balloon inflation, mobile components were seen hanging from the luminal surface of the aorta, which were not present on imaging before balloon placement (Figure 1C).

Pulsed and color flow Doppler demonstrated a retrograde diastolic flow velocity in the arch and distal ascending aorta during intraaortic balloon counterpulsation, as well as a systolic increase in flow velocity after balloon deflation (Figure 2).

Evaluation of coronary flow augmentation: The left main, proximal left anterior descending and circumflex arteries were imaged in each patient (Figure 3). The coronary flow pattern was usually biphasic, consisting of a small systolic component followed by a larger diastolic component. With intraaortic balloon counterpulsation, peak diastolic flow velocity increased (Figure 4) by a mean of 117% (range 62 to 287), and the flow velocity integral increased by a mean of 87% (range 43 to 176) compared with those of the immediately preceding nonaugmented beat. Changes in peak flow velocity and flow velocity integral with augmentation were statistically significant ($p = 0.002$ and 0.003, respectively; Table I). In patient 5, premature deflation of the balloon was diagnosed in 2 ways. Color flow M-mode Doppler of the aortic arch showed that the retrograde diastolic flow caused by balloon inflation ended before the QRS (Figure 5A). Similarly, pulsed Doppler of the left coronary artery flow showed early termination of augmented diastolic coronary flow before the QRS (Figure 5B).



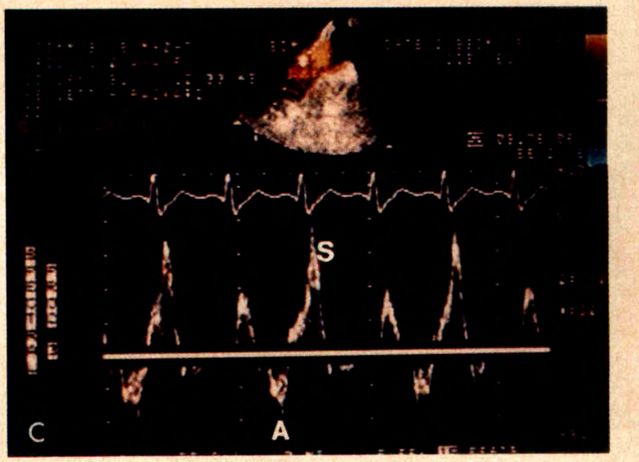


FIGURE 2. Transesophageal color flow and pulsed Doppler imaging of distal ascending aorta and aortic arch. *A,* color M-mode through ascending aorta during 1:1 balloon augmentation reveals anterograde red flow during systole (S) alternating with retrograde blue flow during diastole (D). *B,* transition from 1:1 to 2:1 augmentation *(right of arrow)* shows anterograde red flow throughout cardiac cycle during nonaugmented beat (NA), whereas retrograde blue flow is seen across entire aorta during diastole only on every other beat, which is augmented (A). *C,* augmented retrograde diastolic flow (A) on every other beat during 2:1 augmentation is confirmed by pulsed Doppler. Also note increased systolic flow velocity (S) on every other beat only after balloon deflation, reflecting systolic unloading.

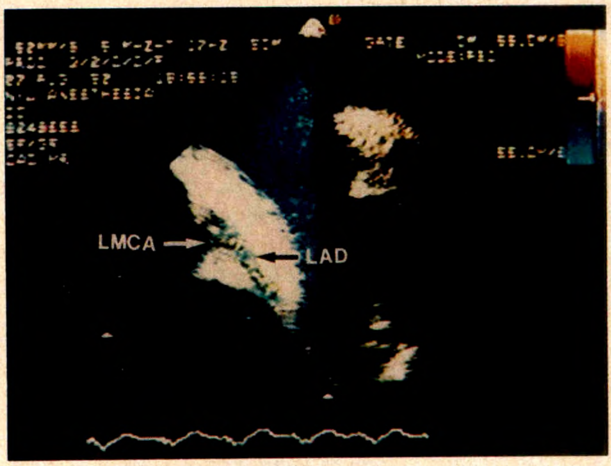


FIGURE 3. Transesophageal image of left coronary artery with mosaic color pattern representing turbulent flow during counterpulsation. LAD = left anterior descending; LMCA = left main coronary artery.

DISCUSSION

Among the goals of intraaortic balloon counterpulsation are the augmentation of peripheral perfusion and diastolic coronary arterial blood flow.[14] Until recently, the measurement of phasic coronary blood flow needed invasive techniques that may be impractical. This study presents an innovative and potentially useful application of transesophageal echocardiography in assessing placement and function of the intraaortic balloon pump. We made the following observations: (1) The left coronary artery can be visualized by transesophageal echocardiography in patients needing balloon pumping, and flow velocity within the artery can be recorded by pulsed Doppler. (2) Augmentation of diastolic coronary flow velocity during balloon inflation can be observed. (3) Systolic increases in anterograde aortic blood flow velocity after balloon deflation can be seen. (4) The intraaortic balloon can be seen within the descending thoracic aorta, and its correct position can be verified. (5) The relation between the size of the balloon and the aortic diameter can be determined. (6) Suboptimal balloon inflation/deflation timing can be diagnosed. (7) Complications of the balloon/aortic wall interaction can be assessed.

Observations on coronary flow augmentation: Left coronary artery blood flow is detectable by transesophageal Doppler echocardiography in 77 to 86% of patients.[6–8] The flow pattern obtained using this technique is analogous to that determined by invasive methods. The normal flow pattern is biphasic with systolic and diastolic peaks (higher in diastole [approximately 0.6 m/s] due to the higher diastolic perfusion gradient between the aorta and left ventricle). Yamagishi et al[6]

TABLE I Coronary Blood Flow During 2:1 Intraaortic Balloon Counterpulsation

	V Peak (cm/s)			FVI (cm)		
Pt.	NA	A	% Incr.	NA	A	% Incr.
1	72	117	62%	17.5	28	60%
2	45	81	80%	10.1	16.9	67%
3	22	86	287%	8.3	22.5	176%
4	29	53	82%	8.5	13.5	58%
5	26	58	123%	5	11	120%
6	40	67	68%	14	20	43%
Mean	39	77*	117%	10.5	18.6†	87%

*p = 0.002 (augmented vs nonaugmented); †p = 0.003 (augmented vs nonaugmented).

A = augmented; FVI = flow velocity integral; % Incr. = percent increase; NA = nonaugmented; V = velocity.

previously observed the alteration of coronary flow in 3 patients during intraaortic balloon pumping using transesophageal pulsed Doppler. Our data showed a mean increase in peak left coronary artery flow velocity of 117%. Furthermore, we calculated the flow velocity time integral, which is reflective of the volume of blood flowing through the sample volume during a cardiac cycle. This increased by a mean of 87% during counterpulsation.

Invasive studies of coronary blood flow during counterpulsation were previously reported.[3-5] Most methods measure coronary sinus flow in right heart bypass preparations, or great coronary vein flow with thermodilution catheters. Results range from no change to a 50% increase in coronary flow during counterpulsation. These disparate findings have been attributed to the variability in pressure-dependent flow and autoregulation that is seen in different coronary beds. Our study reflects beat-to-beat variability in coronary blood flow in proximal, nonstenotic coronary arteries where flow is likely to be largely pressure dependent. Powell et al[3] showed that the effects of intraaortic counterpulsation on total coronary blood flow are most evident when myocardial performance and coronary blood flow are most severely impaired. This parallels our study in which the most hemodynamically impaired patient (patient 3) demonstrated the highest increase in peak coronary flow velocity and flow velocity integral during counterpulsation. Counterpulsation increased diastolic blood pressure from 30 to 80 mm Hg in this patient. Thus, variable degrees of hemodynamic compromise may account for the wide range in flow augmentation among the 6 patients in our study.

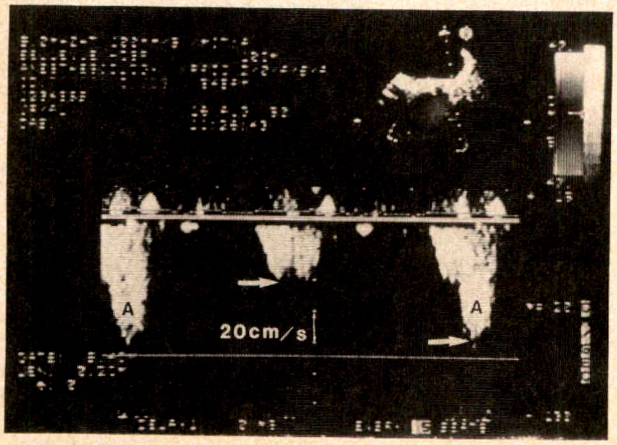


FIGURE 4. Transesophageal pulsed Doppler spectral analysis of flow in proximal left coronary artery during 2:1 intraaortic balloon counterpulsation. Note marked increase in coronary flow velocity during 2 augmented cycles (A) in comparison with nonaugmented cycle (center beat).

Observations of balloon pump position and occlusivity: Optimum positioning of the intraaortic balloon for maximum augmentation of mean arterial diastolic pressure is ideally as close to the aortic valve as possible.[15,16] However, the risk of occlusion of the great vessels dictates that the correct positioning be distal to the left subclavian artery. Correct placement is accomplished under fluoroscopy or by externally measuring from the point of insertion to the sternal angle. Two-dimensional transesophageal echocardiography can accurately guide balloon placement. In 1 of our cases, repositioning of a balloon that had been placed in the transverse aorta was accomplished with such guidance.

The importance of balloon volume displacement on augmentation of aortic diastolic pressure and coronary blood flow has been shown experimentally.[4,16] Using a distensible intraaortic balloon, Weber et al[16] observed

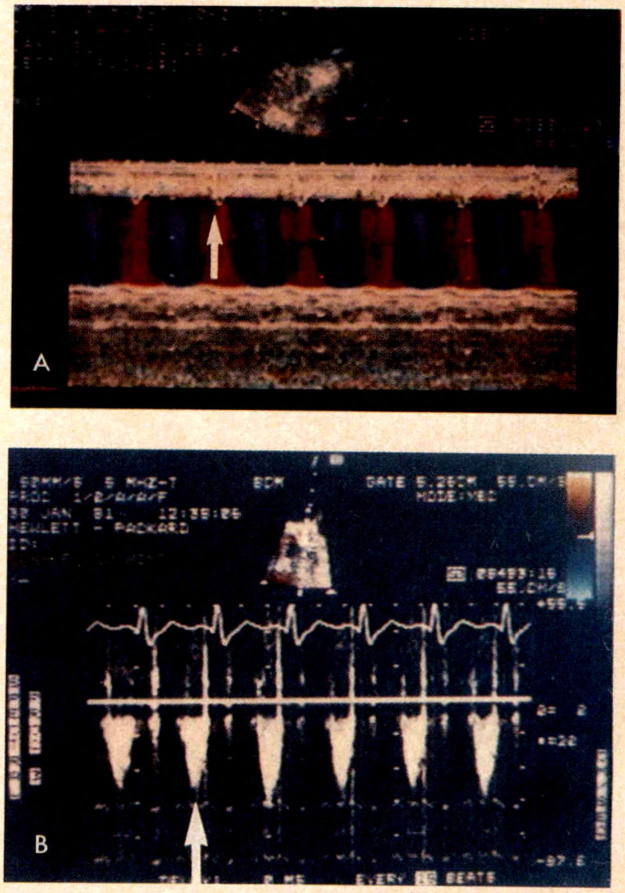


FIGURE 5. Transesophageal echocardiography. *A,* color flow Doppler of aortic arch. Note that augmented, retrograde diastolic flow *(blue)* ends prematurely before electrocardiographic R-wave peak *(arrow)*, reflecting early balloon deflation. *B,* pulsed Doppler of left coronary artery. Note that coronary blood flow in diastole *(arrow)* also ends prematurely before electrocardiographic R-wave peak, reflecting early balloon deflation.

that the greatest augmentation in diastolic pressure was seen with complete occlusion of the aorta by the balloon. Because aortic size for any subject is seldom known, the choice of balloon diameter is somewhat arbitrary. Transesophageal echocardiography may provide an in vivo method for measuring aortic diameter and assessing occlusivity.

Observations regarding complications of the intraaortic balloon: Damage to the aorta (including dissections, lacerations and subadventitial hematomas) has been reported.[17-23] Transesophageal echocardiography is a sensitive technique for evaluating such damage. Freely mobile echodensities resulting from disrupted atherosclerotic plaque were seen in 2 of 6 patients along the aortic luminal surface in the area of balloon inflation. We hypothesize that these may be the source of the peripheral embolization that may occur during counterpulsation. Recent transesophageal echocardiographic studies showed an association between similar mobile densities in the aorta and embolic disease.[24-27]

Study limitations: Although our observations suggest the possible use of transesophageal echocardiography in evaluating intraaortic balloon placement and function, the efficacy of this technique in a larger group of patients needs to be addressed. We do not have independent corroboration of our Doppler findings, because there was no invasive measurement of coronary flow or transmyocardial perfusion pressure. Furthermore, we were measuring flow velocities rather than actual flow. Assuming that the coronary artery diameters at the level of the sample volume did not change with augmentation, the increase in flow velocity would translate to an increase in flow. We observed no gross changes in artery diameter. Furthermore, because the incident Doppler beam may not be precisely parallel to the vessel direction, blood flow velocities measured by this approach can be underestimated. However, our interest is mainly in the change in coronary flow velocity caused by counterpulsation, rather than in the absolute flow velocity. Because there was no change in either angulation of the incident Doppler beam or position of the sample volume within the coronary artery between 2 successive beats, the percent change in the flow velocity time integral between a nonaugmented cycle and the subsequent augmented cycle reflects the volume of additional blood flow attributed to counterpulsation.

Clinical implications: This study demonstrates the use of a relatively noninvasive technique in evaluating intraaortic balloon positioning and monitoring coronary artery blood flow velocity during counterpulsation. This may be especially useful in unstable patients in whom balloon placement can be performed at bedside under transesophageal echocardiographic guidance. Furthermore, because transesophageal echocardiography is often used during cardiac surgery, it may also provide benefits during operations in which balloon pumping is needed. Whereas hemodynamic parameters of improved peripheral perfusion are usually used to confirm balloon pumping efficacy, transesophageal echocardiography may add another dimension to our objective measures of balloon function. By recording the effects on coronary blood flow velocity, the diastolic timing of balloon inflation can be adjusted to maximize flow during augmentation.

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Excimer Coronary Laser Angioplasty: It's Time for a Critical Evaluation

Garrett Lee, MD, and Dean T. Mason, MD

With the initial demonstration of laser in coronary artery disease,[1,2] several experimental animal and clinical studies have been conducted in the past decade to determine the potential of coronary laser angioplasty. The principal impetus for the laser as well as for all other non-balloon interventional devices is to combat the severe sequelae following percutaneous transluminal balloon angioplasty (PTCA), namely restenosis. Early clinical investigations involved using continuous-wave lasers such as argon or neodymium: yttrium-aluminum-garnet (YAG) transmitted via a silica fiber and exiting the tip as a free beam[3] or heating a metal probe.[4] These lasers and laser-heated probes not only effect thermal damage to the obstructed site but also its adjacent area, including the vessel wall. Such effects have caused concerns that continuous-wave lasers would potentially increase the frequency of coronary spasm, vessel thrombosis, and luminal wall injury such as dissection, aneurysm and perforation.[5,6] The excimer laser, however, is a pulsed laser, and is believed to be more ideal for excimer coronary laser angioplasty (ECLA) because it ablates atherosclerotic plaque obstruction by a nonthermal mechanism,[7] thus anticipating lower complication and restenosis rates. This communication examines whether present excimer laser systems have achieved the potential of safe and effective coronary angioplasty.

Excimer lasers and coronary delivery systems: The excimer laser is comprised of a gas as its lasing medium. There are 4 excimer gases each of which produces a different ultraviolet wavelength (i.e., argon fluoride 193 nm, krypton fluoride 248 nm, xenon chloride 308 nm, and xenon fluoride 351 nm). Excimer stands for "excited dimer" and connotes 2 atoms in an excited state in the lasing medium. ECLA cannot take advantage of the shorter ultraviolet wavelengths (e.g., 193 and 248 nm) because it cannot be transmitted down a silica fiber (transmission range from 300 to 2,100 nm). The xenon chloride excimer laser (308 nm) is mostly utilized in angioplasty investigations and is generally operated between 100 and 250 mJ at 20 to 40 Hz. However, the pulse energy of the xenon chloride light has to be modified by prolonging the pulse width and thereby reducing peak power per pulse in order to conduct the energy through a silica fiber without damage to the fiber. Thus, the limitation of present fiberoptic delivery system has affected the use of the full capability of the excimer laser.

The fiberoptic catheter delivering the excimer laser is usually several quartz fibers arranged concentrically around a central lumen large enough for a guidewire (0.014 to 0.018 inch) to pass. Investigators have been using 20 to 40 fibers (100 μm each) around a central lumen. The design of present catheter systems is flawed because of the presence of dead space between fibers which have contributed to inadequate tissue ablation, and possibly leading to mechanical injury to the vascular wall. The outer diameter of the catheter varies from 1.3 to 2.0 mm. The energy fluence out the end of the catheter varies from 30 to 60 mJ/mm^2. Newer catheters have 200 smaller fibers (50 μm each) to minimize the dead space between fibers. However, it remains to be determined whether the smaller diameter fibers will provide the optimal energy fluence as the larger diameter fibers.

In general, the ECLA procedure involves standard angioplasty technique by the percutaneous femoral approach. An 8 or 9Fr guiding catheter is inserted, and after manipulating and extending the guidewire across the lesion into the distal coronary artery, the fiberoptic laser catheter is advanced over the wire to the lesion. A small amount of contrast is injected to confirm the position of the laser catheter in direct contact with the face of the obstruction. The excimer laser is activated while the catheter is slowly advanced through the lesion. The lesion may also be irradiated on slow pullback of the catheter. After angiographic study, the lasing process can be repeated. Based on the severity of the remaining stenosis, it is noteworthy that additional PTCA is usually required after laser treatment. Standard pharmacologic agents are administered as in all PTCA procedures.

Controversy on the benefits of excimer coronary laser angioplasty: Advocates of excimer lasers claim that it can precisely cut through atheroma by photodecomposition without producing any thermal injury,[7] thus decreasing the thrombogenic potential by leaving a smooth uncharred lumen.[8] However, laboratory experiments have shown that thermal probes had fewer platelets adhering to the treated surface than at sites treated by the excimer.[9] It is possible that the thermal damage to the intraluminal wall renders its surface unrecognizable to adherent platelets. Arterial spasm is also thought to be a less likely occurrence due to its nonthermal lasing effect,[10] but in the clinical setting, spasm has not been eliminated and has continued to be a troublesome problem.[11]

It is also believed that the excimer laser can ablate calcified plaque in a rapid manner, but this requires high-energy density at high repetition rates. High repetition rates (e.g., 100 Hz) can produce thermal injury because the surrounding tissue cannot dissipate the heat

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TABLE I Multicenter Studies on Excimer Coronary Laser Angioplasty[17–19]

	1st Study	2nd Study	3rd Study	Total
No. of patients	1,570	223	100	1,893
No. of coronary lesions	1,917	245	100	2,262
LAD	786 (41%)	138 (56%)	67 (67%)	991 (44%)
Right	518 (27%)	63 (26%)	21 (21%)	602 (27%)
LC	326 (17%)	30 (12%)	7 (7%)	363 (16%)
BG	268 (14%)	14 (6%)	5 (5%)	287 (13%)
Sole laser treatment	652 (34%)	—	38 (38%)	—
Laser-assisted PTCA	1,265 (66%)	223 (91%)	52 (52%)	1,540 (68%)
Proced. success	1,397 (89%)	192 (78%)	90 (90%)	1,679 (89%)
Proced. complications				
Death	6 (0.4%)	3 (1.4%)	0	9 (0.4%)
Nonfatal MI	46 (2.9%)	8 (3.6%)	0	54 (2.9%)
Emerg. bypass	53 (3.4%)	7 (3.1%)	3 (3%)	63 (3.3%)
Dissection	220 (14%)	20 (8.9%)	30 (30%)	270 (14.3%)
Spasm	—	—	16 (16%)	—
Acute occlusion	113 (7.2%)	5 (2.4%)	5 (5%)	123 (6.5%)
Perforation	28 (1.8%)	3 (1.4%)	6 (6%)	37 (1.9%)

BG = bypass graft; Emerg. = emergency; LAD = left anterior descending; LC = left circumflex; MI = myocardial infarction; Proced. = procedural; PTCA = percutaneous transluminal coronary angioplasty.

TABLE II Comparison of the Procedural Complications and Chronic Restenosis Rates of Excimer Laser Angioplasty (ECLA) with PTCA[17–19,23,30–32]

	ECLA (%)	PTCA (%)
Death	0.4	1
Nonfatal MI	3	4
Emergency bypass	3	4
Dissection	14	5
Acute occlusion	7	5
Perforation	2	0.1
Chronic restenosis	45	30

Abbreviations as in Table I.

energy fast enough between pulses. Transmission of excimer through fiberoptics to ablate directly the path of heavily calcified plaque obstruction in humans remains to be demonstrated. Low repetition rates (e.g., 10 and 20 Hz) would allow the tissue adequate time for the temperature to return to baseline, thus avoiding significant lateralization of injury, but may not be sufficient to ablate calcified lesions. Moreover, in contrast to the continuous-wave argon laser, pulsing with an excimer can induce large particulate debris which can embolize.[12]

The excimer laser is claimed to be the ideal laser for coronary angioplasty because it decreases the risk of vascular wall injury, but this attribute has not been demonstrated.[13] The available fiberoptic catheters for excimer delivery are still quite crude for the delicate human coronary artery. It is unclear whether there is some Dottering effect that takes place while the laser catheter is passed through the obstruction.[14] Furthermore, the excimer laser system is expensive (cost at least $200,000), and the use of ultraviolet radiation has been shown to damage the deoxyribonucleic acid molecular structure in the cell.[15] Because of its potential mutagenicity, some investigators urge caution and call for more data to justify any medical use of the 308 nm laser.[16] Although it is unlikely that a single exposure to ultraviolet radiation would be carcinogenic, multiple or repeated exposures and widespread use to large numbers of patients should remain a concern.

CLINICAL STUDIES

Multicenter trials: Three large studies involving ECLA are taking place. The largest multicenter study comprises 1,917 coronary lesions from 1,570 patients.[17] Forty-one percent of lesions treated involved the left anterior descending artery, 27% the right coronary artery, 17% the left circumflex artery, 14% saphenous vein bypass grafts, and 2% the left main artery. Mean arterial stenosis decreased from a baseline of about 86 to 48% after laser angioplasty. Procedural success defined as >20% increase in luminal diameter with the laser was 89%. In two-thirds of lesions, further dilatation was required using the balloon catheter which reduced the stenosis to 25%. The excimer laser was used as sole therapy in the remaining one-third.

The second large multicenter study included 223 patients and 245 stenoses.[18] Procedural success with the laser was 78%. Almost all lesions were treated after the laser application by balloon angioplasty to achieve a larger luminal diameter. Because of high risks, current excimer systems cannot ablate total atherosclerotic occlusion, and lasing subtotal obstruction cannot be performed without successful transstenotic preplacement of a guidewire.

The European multicenter registry recently reported its results in the first 100 patients.[19] Coronary dissection and perforation were high at 16 and 6%, respectively. The study population characteristics, procedural success rates, complications, and related information from the 3 multicenter trials are listed in Table I.

Complications: The complication rates for death, nonfatal myocardial infarction, and emergency coronary artery bypass graft surgery were 0.4, 2.9 and 3.4%, respectively, in the first large study,[17] and 1.4, 3.6 and 3.1%, respectively, in the second multicenter study.[18] The complication rates for dissection, abrupt occlusion and perforation were 14, 7.2 and 1.8%, respectively, in the first study[17] and 8.9, 2.4 and 1.4%, respectively, in the second.[18] Longer lesions (>1 cm) and complex lesions did not appear to be associated with increased risk of adverse events.[17,20] High rates of coronary spasm from 8.5 to 53% were reported in several trials.[11,19,21,22]

Restenosis rates: The 6-month restenosis rate (generally defined as loss of more than one-half gain in lumen diameter and final stenosis of >50%) reported from the excimer laser registry was about 45%.[23] The more severe the initial lesion or the less patent angiographic result after laser treatment, the higher the restenosis rate. Other smaller studies have also reported a restenosis rate from 41 to 69%.[24–27] Stand-alone or sole ECLA does not reduce the restenosis rate[27]; adjunctive balloon angioplasty also does not affect restenosis.[28]

Comparison with percutaneous transluminal coronary angioplasty: Any new interventional device should attempt to match or improve on the short- and long-term efficacy, safety, and cost-effectiveness of PTCA. Excimer laser radiation removes atherosclerotic plaque by photodecomposition, whereas PTCA dilates the stenotic lumen by fracturing the plaque. Both procedures can cause intraluminal vascular wall injury.[29] ECLA appears to have similar complication rates as the National Heart, Lung, and Blood Institute PTCA registry in terms of death, nonfatal myocardial infarction, and emergency coronary artery bypass graft surgery (PTCA: 1, 4 and 4%, respectively).[30] However, the complication rates of excimer angioplasty were seemingly higher than PTCA for dissection, spasm, abrupt occlusion and perforation (PTCA: 5, 1, 5 and 0.1%, respectively)[30,31] (Table II). The excimer laser did not decrease the complication rate of balloon angioplasty.

In more than two thirds of lesions, the balloon catheter had to be applied after excimer laser treatment to obtain an adequate result in luminal patency. Thus, at the present time, use of the laser has not reduced the cost of coronary angioplasty; PTCA is performed in conjunction with the excimer laser. Interestingly, the balloon catheter can be used to repair the high dissection rate after excimer laser angioplasty.[22,27] Furthermore, the coronary restenosis problem has not been solved with the application of excimer laser; the laser did not reduce the 30% restenosis rate after balloon angioplasty[32] and, in fact, the post-ECLA restenosis rate was substantially higher (45%).

Potential indications and limitations: In a small study of 100 patients from a single center, it is believed that excimer laser angioplasty is effective and safe for lesions not ideal for balloon angioplasty, such as long and diffuse disease, calcified lesions, ostial stenoses, lesions that involve major side branches, and stenoses that cannot be crossed or dilated with a balloon.[33] However, this study had limitations in that it was only an acute study, and follow-up complications were not reported. Furthermore, this was not a randomized controlled trial.

Current laser and catheter systems are effective in creating a tiny coronary opening in the stenotic lumen after guidewire placement. The contribution of the catheter's Dottering effect is unclear. Adjunctive balloon angioplasty is still required to further enlarge the lumen. The acute and long-term salutary results of ECLA need to match or exceed that of conventional PTCA. Randomized controlled studies are necessary to determine whether excimer angioplasty is really a bona fide alternative to PTCA, and whether the excimer laser will be replaced by other less expensive pulsed lasers such as neodymium:YAG or holmium:YAG lasers. The safety of laser angioplasty may be enhanced by coupling to ultrasonographic, angioscopic or fluorescence spectroscopic technologies. Despite these advances, the excimer angioplasty long-term restenosis rate will probably remain high or higher than PTCA. It may be imperative to find and use pharmacologic agents such as new antithrombotic drugs or new antiproliferative agents to combat the restenosis problem.

In conclusion, current excimer laser systems cannot be relied upon to open a total coronary atherosclerotic occlusion or even a subtotal obstruction without the initial successful passage of a guidewire. The over-the-wire fiberoptic catheter can reduce the stenotic lumen by about 30 to 40%. When compared with balloon angioplasty, the laser produces a higher frequency of dissection and perforation, and it does not decrease the complication rate of PTCA. After excimer treatment, the balloon catheter is usually required to further enlarge the lumen, and may even repair the dissection caused by the laser. The 6-month restenosis for excimer angioplasty is about 45%, and adjunctive balloon angioplasty does not affect the restenosis rate. Failing to reduce the restenosis rate, the proponents of the excimer laser now claim ECLA to be more suitable than PTCA in long and diffuse disease, very tight stenoses, ostial lesions, calcified lesions, and lesions that have major side branches, but limitations exist and randomized studies are needed to substantiate these claims. Given the expense of the excimer laser, the costs of the combined ECLA and PTCA procedure, the use of current excimer laser catheters, and the inherent nature and extent of immediate complications and the high frequency of chronic restenosis, the excimer coronary laser remains a research tool of uncertain special value. Further development and research studies are needed before it can achieve a place in today's coronary angioplasty technology.

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Syndromes X: Two Too Many

Norman M. Kaplan, MD

Not long ago, an article appeared in *The Lancet* describing "Syndrome X" in patients with "Syndrome X," the former representing hyperinsulinemia, the latter microvascular angina.[1] Although some letter writers subsequently applauded the "diagnostic economy . . . of syndrome X (being) part of syndrome X,"[2] others found the possibility of all of these features representing only one massive syndrome X to be "rather boring and unconfusing."[3]

As one who deals with both X syndromes, I urge all who describe them to cease and desist in the use of such sloppy, poorly understood terminology and to state, simply and clearly, what is meant: *Insulin resistance syndrome* for a constellation of dyslipidemias, predominantly upper body obesity, diabetes mellitus, and hypertension, which are likely interconnected by the hyperinsulinemia that results from peripheral muscle resistance to insulin; and ***angina with normal coronary arteriography*** for exertional angina with a positive exercise test but normal coronary arteries by angiography.

Confusion about insulin resistance syndrome: Dr. Gerald Reaven,[4] in 1988, was likely the first to publicly use syndrome X for the metabolic constellation. Since then, the syndrome has been called by many names (Table I).

Dr. Reaven called attention to the "enormous importance of these related variables in the genesis of coronary artery disease" but he did not suggest that his metabolic syndrome X could be responsible for the cardiac syndrome X.

Confusion about angina with normal coronary arteriography: Dr. H. Kemp[5] is given credit for having first used the name syndrome X for angina with normal coronary arteriography, in 1973. Since then, a number of terms have been used to describe various features of the

TABLE I Names Used for the Insulin Resistance Syndrome

Syndrome X
The deadly quartet
Reaven's syndrome
Metabolic cardiovascular syndrome
Metabolic angiopathic syndrome
Familial dyslipidemic hypertension
Glucose intolerance, obesity, hypertension
Waist-hip ratio syndrome

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TABLE II Names Used for Angina with Normal Coronary Arteriography

Syndrome X
Microvascular angina
Reduced dilatory capacity of coronary microcirculation
Impaired coronary vasodilator reserve
Myocardial ischemia with reduced coronary perfusion reserve
Abnormal coronary blood flow reserve
Coronary adrenergic hyperreactivity
Abnormal coronary vasomotion

syndrome (Table II). There is obviously no agreement on what the underlying cause(s) of the cardiac syndrome may be. There appear to be multiple mechanisms including impaired vasodilation and abnormal vasomotion.

Does insulin resistance syndrome lead to angina with normal coronary arteriography?: Dean et al[1] found significantly higher high-density lipoprotein cholesterol and postglucose-load plasma insulin levels in 11 patients with typical effort angina and normal coronary arteriograms compared with 11 healthy subjects who were closely matched for age, sex and body mass index. They suggested that hyperinsulinemia could lead to coronary (and generalized) microvascular dysfunction and concluded that, "The disorder may represent one part of a clinical spectrum of microvascular diseases, which includes diabetes and hypertension, in which high immunoreactive insulin concentrations may be pathogenetic."

In the letters to the editor of *The Lancet*, Godsland and Oliver[6] chided Dean et al for "not putting their observations into the much broader context of the association between hyperinsulinemia and coronary heart disease," citing R. Stout's review of multiple studies showing a positive relation between the 2. In response to Godsland and Oliver, Dean et al[7] agree "that 'Metabolic Syndrome X' does indeed have some features that may be common to the syndrome X long familiar to cardiologists." They end their rebuttal by stating that, "We applied the term, carefully defined, in deference to this usage but deleted reference to the metabolic version because *The Lancet* suggested that it might confuse."

Conclusion: I agree with the editors of *The Lancet*. However, I think they did not exert all of the needed editorial supervision: Better to have precluded the use of even 1 syndrome X. Now that the 2 have been crossed, it is high time to throw them both out and call syndromes by meaningful, unambiguous, descriptive names. Down with syndromes X, up with insulin resistance syndrome and angina with normal coronary arteriography. Even if the 2 are sometimes or often found in the same patients, they are 2 distinct clinical syndromes and they deserve proper names.

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Editorial Board Meeting of *The American Journal of Cardiology* on 14 April 1992

The annual editorial board meeting of *The American Journal of Cardiology* (AJC) in 1992 was held in Dallas, Texas, on April 14 at the time of the Annual Scientific Sessions of *The American College of Cardiology*. The major purposes of the meeting were to say "thanks" to the 164 board members for their enormous help during the previous year, to pay particular tribute to the board members reviewing the most manuscripts in 1991, and to receive input from board members through questions and comments.

1. Introduction of new board members: Fifteen physicians (Table I) were added to the board beginning January 1992, and they were introduced. New board members are selected entirely on their record as non-board reviewers for the AJC. It is relatively easy to select the new board members. The card files of the 1,400 or so non-board AJC reviewers are reviewed and the 15 or so with the best reviewing records are selected. Usually about a similar number of members are eliminated from the board. In 1991, however, all board members did such a superb job that none could be readily removed. In the future some infrequently- or inadequately-used board members will have to be eliminated to make room for the many non-board reviewers deserving of board status.

2. Number of manuscripts sent for review to board members in 1991: A total of 1,615 manuscripts were received in the Bethesda, Maryland, editorial office in 1992 (This number does not include the manuscripts for the supplement issues.), and 984 of them were sent to the 4 types of specialists on the board (Table II). Of the 984 manuscripts, an average of 6.0 per board member, 938 (95%) were reviewed on time (3 weeks from the mailing date to the receiving date), only 18 (2%) were not reviewed within the 3-week period, and 45 manuscripts (4%) were returned without review.

3. AJC board members reviewing the most manuscripts in 1991: The top 16 reviewers in 1991 are listed in Table III; of the 235 manuscripts reviewed by these 16 members, the reviews in 228 (97%) were returned on time. Table IV lists the 19 board members reviewing 9 or 8 manuscripts in 1991; of the 159 manuscripts reviewed by them, all reviews were received within the 3-week time period. Table V lists the 22 members who each reviewed 7 manuscripts in 1991; of the 154 manuscripts reviewed, 150 (97%) were reviewed on time. The reviewing records of these 62 board members (representing 38% of the board members) is truly remarkable!

4. Numbers of pages and articles and types of articles published in the AJC in 1991: These data are presented in Table VI. A total of 680 articles were published on 3,165 pages in 1991, an average of 57 articles a month, with each having an average length of 4.65 pages. These numbers represent a 5% increase (3,001 to 3,165) in the numbers of pages for articles and a 3% increase (662 to 680) in the numbers of articles published in 1991 compared to 1990. The reasons for the increase in articles published in 1991 was a 13% increase in the number of brief reports (158 to 182) published, a 6% decrease in the numbers of long reports (448 to 421) published, and a 5% increase in the numbers of pages published. An editorial stylistic change was made in the *Journal* beginning April 15, 1991, and this change resulted in an approximately 15% decrease in the content per page on the pages without tables or figures. The size type used and the space between lines were

TABLE I New Editorial Board Members Beginning January 1992

1. Daniel S. Berman
2. Robert M. Califf
3. S. Ward Casscells, III
4. John Douglas
5. David Faxon
6. Nancy C. Flowers
7. Victor F. Froelicher, Jr.
8. Stephen P. Glasser
9. Joseph Loscalzo
10. Richard C. Pasternak
11. John S. Schroeder
12. Prediman K. Shah
13. Burton Sobel
14. George W. Vetrovec
15. William B. White

TABLE II Numbers and Types of Manuscripts Sent to AJC Board Members According to Specialty of Board Member

Specialty	Number on Board	No. MSs Sent (No./Reviewer)	No. LR	No. BR	No. CR	No. (%) Reviews on Time	No. (%) Reviews Late	No. (%) MSs Returned Without Review
Adult cardiologist	131	836 (6.4)	805	24	7	785 (94%)	16 (2%)	35 (4%)
Pediatric cardiologist	15	91 (6.1)	80	11	0	85 (93%)	1 (1%)	5 (6%)
Cardiac surgeon	13	37 (2.8)	33	2	2	34 (92%)	0	3 (8%)
Radiologist or pathologist	5	20 (4.0)	20	0	0	17 (85%)	1 (5%)	2 (10%)
TOTALS	164	984 (6.0)	938 (95%)	37 (4%)	9 (1%)	921 (94%)	18 (2%)	45 (4%)

BR = brief report; CR = case report; LR = long report; MSs = manuscripts.

returned to the pre-April 15, 1991, format in January 1992. Thus, 1992 should show an increase in number of articles published if the number of pages published remains at the same level as in 1991. The types of long reports published in 1991 are shown in Table II.

5. Symposia published in the AJC in 1991: Nine symposia were published in 1991, a 45% decrease (20 to 9) from 1990 (Table VII). Each symposium is published under separate white cover from the regular issues which are published under blue cover.

6. Numbers of manuscripts submitted in 1991 and the acceptance rate: Table VIII summarizes the numbers of manuscripts submitted to the AJC in each of the last 5

TABLE III Top AJC Board Reviewers in 1991 and Number of Manuscripts Reviewed

Name	No. MSs Reviewed	LR	BR	CR	No. Reviewed on Time
1. Joseph S. Alpert	14	14	0	0	14
2. Eric J. Topol	13	12	1	0	13
3. Peter C. Block	12	12	0	0	12
3. Richard O. Cannon, III	12	12	0	0	12
3. Pamela S. Douglas	12	10	2	0	12
3. L. David Hills	12	12	0	0	12
3. Joel Morganroth	12	10	2	0	12
8. J. Thomas Bigger, Jr.	11	9	2	0	9
8. Michael H. Crawford	11	11	0	0	11
8. David R. Holmes, Jr.	11	10	1	0	11
8. Fred Morady	11	10	1	0	11
8. Arthur J. Moss	11	11	0	0	10
8. Bramah N. Singh	11	10	1	0	11
8. James E. Lock	11	8	3	0	8
8. Lowell W. Perry	11	8	3	0	11
16. George A. Beller	10	10	0	0	10
16. Robert O. Bonow	10	10	0	0	9
16. Gregory J. Dehmer	10	10	0	0	10
16. Richard B. Devereux	10	9	0	1	10
16. George A. Diamond	10	10	0	0	10
16. Nanette K. Wenger	10	9	1	0	10
TOTALS (21)	235	217 (92%)	17 (7%)	1 (<1%)	228 (97%)

Abbreviations as in Table II.

TABLE IV Reviewers of 9 and 8 Manuscripts for the AJC in 1991

Name	No. MSs Reviewed	LR	BR	CR	No. Reviewed on Time
22. Pablo Denes	9	9	0	0	9
22. Robert L. Feldman	9	9	0	0	9
22. Gary S. Francis	9	9	0	0	9
22. Leonard N. Horowitz	9	9	0	0	9
22. Jeffrey M. Isner	9	8	1	0	9
22. Natesa Pandian	9	7	1	1	9
22. David H. Spodick	9	9	0	0	9
29. Bernard R. Chaitman	8	8	0	0	8
29. Kanu Chatterjee	8	8	0	0	8
29. John P. DiMarco	8	7	1	0	8
29. Joseph A. Franciosa	8	8	0	0	8
29. Bernard Gersh	8	7	1	0	8
29. Abdulmassih S. Iskandrian	8	8	0	0	8
29. Carl V. Leier	8	8	0	0	8
29. Jawahar Mehta	8	7	0	1	8
29. Eugene R. Passamani	8	8	0	0	8
29. Florence H. Sheehan	8	8	0	0	8
29. James T. Willerson	8	8	0	0	8
29. A. Rebecca Snider	8	8	0	0	8
TOTALS (19)	159	153 (96%)	4 (3%)	2 (1%)	159 (100%)

Abbreviations as in Table II.

TABLE V Reviewers of 7 Manuscripts for the AJC in 1991

Name	No. MSs Reviewed	LR	BR	CR	No. Reviewed on Time
41. William E. Boden	7	7	0	0	7
41. Agustin Castellanos	7	7	0	0	7
41. William H. Gaasch	7	7	0	0	7
41. Julius M. Gardin	7	7	0	0	7
41. Robert E. Goldstein	7	7	0	0	7
41. Sidney O. Gottlieb	7	7	0	0	7
41. William B. Kannel	7	7	0	0	7
41. Kenneth M. Kent	7	7	0	0	6
41. George J. Klein	7	7	0	0	7
41. Frank I. Marcus	7	7	0	0	7
41. Richard S. Meltzer	7	7	0	0	7
41. Franz H. Messerli	7	6	1	0	7
41. Robert J. Myerburg	7	7	0	0	7
41. Robert A. O'Rourke	7	7	0	0	7
41. Carl J. Pepine	7	6	1	0	6
41. Augusto D. Pichard	7	6	1	0	7
41. Bertram Pitt	7	7	0	0	6
41. Philip J. Podrid	7	7	0	0	7
41. Melvin M. Scheinman	7	7	0	0	7
41. David D. Waters	7	7	0	0	7
41. Arthur Garson, Jr.	7	7	0	0	7
41. Barry J. Maron	7	6	1	0	6
TOTALS (22)	154	150 (97%)	4 (3%)	0	150 (97%)

Abbreviations as in Table II.

TABLE VI Numbers of Pages and Articles Published in *The American Journal of Cardiology* in 1991

Number of Pages	3,672			
For Articles		3,165		(86%)
For Readers' Comments		38 (59)*[22]†		(1%)
For Staff, Editorial Board		24		(<1%)
For Contents in Brief		74		(2%)
For Contents with Abstracts		234		(6%)
For Information for Authors		23		(<1%)
For Meeting Abstracts		10		(<1%)
For Volume Indexes		104		(3%)
Number of Articles	680			
Long Reports		421		(62%)
Coronary Artery Disease			203 (48%)	
Arrhythmias and Conduction Disturbances			66 (16%)	
Systemic Hypertension			21 (5%)	
Congestive Heart Failure			16 (4%)	
Valvular Heart Disease			31 (7%)	
Cardiomyopathy			15 (4%)	
Congenital Heart Disease			18 (4%)	
Cardiovascular Pharmacology			2 (<1%)	
Miscellaneous			42 (10%)	
Methods			7 (2%)	
Historical Studies			0	
Brief Reports		182		(27%)
Case Reports		41		(6%)
Editorials		25		(4%)
From-the-Editor columns		11		(1%)

*Numbers of Readers' Comments (formerly Letters to the Editor) published.
†Numbers of replies published.

TABLE VII Symposia Published in *The American Journal of Cardiology* in 1991

	1991 Date of Publication	Subject of Symposium	Guest Editor(s)	Sponsor	No. of Articles	No. of Discussions	No. of Pages	Interval (mos) Symposium to Publication
A	January 25	Adjunctive therapies in thrombolysis	Robert Roberts	Genentech	6	0	32	—
B	April 22	Beta blockers in hypertension	Kikou Arakawa Pieter A. van Zwieten	Sandoz	9	0	50	10
C	May 6	Congestive heart failure	William W. Parmley	ICI Pharmaceuticals	11	3	54	23
D	May 21	Nuclear cardiovascular imaging	Mario S. Verani	Fujisawa Pharmaceutical Company	7	0	56	11
A	July 24	Hypertriglyceridemia	Gerd Assmann Antonio M. Gotto, Jr. Rodolfo Paoletti	Parke-Davis	12	0	42	—
B	September 3	Unstable angina pectoris	Giuseppe Speccia Diego Ardissino William C. Roberts	Boehringer Ingelheim	15	0	141	11
C	November 4	Unstable angina pectoris	James S. Forrester	Marion Merrell Dow	14	0	77	11
D	November 18	Ventricular remodeling and unloading after myocardial infarction	Marc A. Pfeffer Eugene Braunwald	Bristol-Myers Squibb	16	0	131	7
E	December 5	Thrombolytic therapy	Joseph S. Alpert Harvey D. White	Smith Klein Beecham	9	1	48	8

years, and the acceptance rates. In 1991, a total of 1,615 manuscripts were submitted, a 6% decrease compared to the number submitted in 1990, and 680 (42%) were accepted for publication. The acceptance rate averaged 40% for the past 5 years. The only reason this percent is this high is because many of the submitted *long reports* are converted into *brief reports* for publication. Approximately 50% of the brief reports published were originally submitted as long reports. If the AJC did not publish brief reports — and I consider them to be a major feature of the AJC — the acceptance rate in 1991 would have been 31% rather than 42%.

TABLE VIII Numbers of Manuscripts Submitted to AJC in Last Five Years (Excludes Symposia)

Year	Number Manuscripts Submitted	Number Manuscripts Published	Percent Published
1987	1,525	695	46%
1988	1,479	636	43%
1989	1,651	526	32%
1990	1,717	662	38%
1991	1,615	680	42%
TOTALS	7,987	3,199	40%

7. Reminder to authors to supply several names with addresses of nonlocal nonbiased reviewers for their manuscripts: Editors have no monopoly on choosing the best reviewers of manuscripts. No one should be more knowledgeable of experts in the subject of a manuscript than the authors of the manuscript. Thus, I urge authors to supply names — preferably 5, and when they are nonboard members their addresses also — of nonbiased, nonlocal potential reviewers for their manuscripts. It is necessary for an author to supply several names because almost certainly some of the potential reviewers will already have a manuscript for review and a second manuscript is not sent to a reviewer who also possesses one, unless the second manuscript is a brief report or a case report. Currently, in only about 20% of manuscripts submitted have authors provided names of potential reviewers. After studying for nearly 10 years reviews by reviewers suggested by authors, I am impressed that the author-suggested reviewers are of high quality and that the author-suggested reviewers are not more biased to a manuscript than are editor-selected reviewers. Indeed, many manuscripts have been reviewed by 1 author-suggested reviewer and by 1 editor-selected reviewer and the author-selected reviewer recommended rejection and the editor-selected reviewer recommended acceptance of the manuscript.

The meeting was then opened to comments and questions from board members:

1. What is the number of paid subscribers to the AJC? These data are published each year in the *Journal* — indeed in all medical journals — in the *Statement of Ownership, Management and Circulation.* This "statement" was published in the November 1, 1991, issue of the AJC. The average numbers of copies of each issue during the preceding 12 months were the following: total copies printed = 32,500 (rounded off to nearest 100); total paid and/or requested circulation = 22,100; free distribution by mail, carrier or other means = 8,600; total distribution = 30,700; copies not distributed = 1,800.

2. How have the Federal Drug Administration guidelines impacted on the AJC? The only effect has been on the number of symposia published, which fell nearly 50% in 1991 compared to 1990. The decrease in numbers of symposia published, however, appears to be a transient one. In 1992, for example, the number of symposia scheduled to be published is similar to the number published yearly before the FDA guidelines were released, namely about 20/year.

3. Why not publish a brief abstract at the beginning of each brief report as is done at the beginning of each long report? The reason this has not been done is to save space. The last paragraph of each brief report, however, should summarize the major message of the report. The brief reports are published in back-to-back format and therefore the insertion of a summary statement at the beginning of each brief report is a bit more cumbersome than is the case with the long reports.

4. Does the AJC use acid-free paper for its editorial pages? Unfortunately, the answer is no. But other major journals including *The New England Journal of Medicine*, *The Journal of the American Medical Association*, *Circulation*, and *The American Heart Journal* are published on acid paper (non-permanent paper). *The Annals of Internal Medicine* switched to acid-free (permanent) paper in November 1991. The consequences of the use of acid paper for editorial pages (defined by many publishers as non-income producing pages) were discussed in a recent editorial in the *Journal*.[1] In my view, it is a disgrace to use acid paper for editorial pages of peer-reviewed medical journals, but I am convinced that alkaline paper will become standard for all peer-reviewed medical publications in the USA by the year 2000 and probably sooner. In January 1987, for example, only 4% of the 3,050 titles of *Index Medicus* were published on acid-free paper. By October 1991, 48% of the titles of *Index Medicus* were known to be published on acid-free paper. In 1987 acid-free paper was in short supply in the USA and 2 manufacturers had a virtual monopoly on it in North America. Today an estimated 35 paper manufacturers provide acid-free paper, such that today it is probably easier to purchase acid-free paper than acid paper. Once paper producers convert from acid to acid-free paper making, it is cheaper, less corrosive to machinery, requires less water, and is less polluting to produce the alkaline paper than the acid paper and for comparable weight paper, the alkaline paper is no more expensive than is the acid paper. Another factor pushing conversion toward alkaline paper is the increased sensitivity or awareness of the problem by paper producers, publishers, authors, and purchasers of print publications. A major impetus toward conversion to acid-free paper has come from the federal government of the USA. In October 1990 Congress passed Public Law 101-423 which requires the use of acid-free paper for publications of enduring value produced by the Government Printing Office, the largest printer in the world. In 1991, 77% of the paper used by the Government Printing Office was alkaline, and by 1996, 100% will be alkaline. Medical publications also should benefit by this law in due course. Many ads in our medical publications are on acid-free paper. Surely our manuscripts deserve to be published on alkaline paper, even if it is of lower weight than that used for the ads. The most productive period of human beings has been the last 140 years and most publications during this period have been on acid paper and therefore they have or soon will vanish into dust. A good quality of toilet paper and paper towels now consists of acid-free paper. Surely if some of our toilet paper can be alkaline, most of our medical publications, including all our peer-reviewed journals, can use a paper of at least similar quality.

5. Is it necessary to publish the Instructions to Authors in each of the 24 issues of the Journal? No. But the 1-page "Instructions" is often used as a filler. I would prefer to shorten the *Contents in Brief*, which occupied 74 pages in 1991, to no more than 1 or 2 pages per issue, as a better page-saving device. Even better would be to drastically reduce or eliminate the *Contents with Abstracts* which occupied 234 pages in 1991.

6. Is the quality of scientific writing getting better? I believe that the quality of the writing by authors from English-speaking countries continues to improve. The problem is that the number of manuscripts being submitted to USA medical journals, including the AJC, by authors residing in countries where the native language is not English is increasing. The latter manuscripts require much editorial effort.

7. Should the abstract format be changed to a structured format which has recently been adapted by The American Journal of Medicine, The Annals of Internal Medicine, Circulation, Journal of the American Medical Association, and The New England Journal of Medicine, among others? These structured formats include separate paragraphs for each of the separate categories, which generally include such items as *background*, *methods*, *results*, and *conclusions* (*New England Journal of Medicine* and *Circulation*), or *objective*, *design*, *setting*, *patients*, *primary outcome measure*, *results*, and *conclusion* (*Annals of Internal Medicine*, *Journal of the American Medical Association*). The addition of the subheadings, and the separation of each subheading into separate paragraphs adds to the length of the abstract. Additionally, there is usually some redundancy in the structured abstracts because each subheading requires at least some statement. Most abstracts in the AJC presently are single paragraphs. I prefer, at least for now, the present AJC abstract format rather than the structured one.

8. Would it be better to have an even right margin for the AJC abstracts or an uneven right margin as it is presently? The uneven right margin was one recommended by a design consultant when the AJC style was changed several years ago. The bold type of the abstract might make the even right margin more cumbersome to achieve than if the type was not of the bold variety. Board members appeared to prefer an even right border for the abstract, and that view appears reasonable to me. An effort will be made to make this change.

9. Should the AJC reestablish the policy of publishing experimental-type studies (those involving non-human animals)? This item was discussed at length at the 1991 board meeting,[2] and this item continues to be a concern of editorial board members. About one half of those members present favored the publication of experimental studies and the other half favored a continuation of the current policy, i.e., the publication of experimental studies only if they are short enough to fit into the brief report section of the *Journal*. The problem is simply that experimental-type manuscripts are usually the longest ones submitted, the numbers of editorial pages available do not predictably increase, and the number of clinical studies submitted remains large. During the first 3 months of 1992 the numbers of manuscripts submitted rose substantially compared to the first 3 months of 1991. If the current numbers continue for all 12 months of 1992, a total of 1,920 manuscripts will be submitted in 1992 and the number of editorial pages available in 1992 is approximately the same as in 1991. If experimental-type manuscripts were accepted, the numbers of clinical studies accepted would decrease, and probably the interval between the acceptance of a manuscript and its publication would increase. Currently, this interval ("lag time") is 3.5 months, and I am convinced that this short interval is a major factor in attracting superb clinical manuscripts into the AJC. Another factor to consider is that the largest numbers of AJC subscribers are private practitioners who probably would find the experimental-type articles of considerably less use to them than the clinical articles. If the publisher were able to provide let's say an additional 200 pages per year on top of the currently budgeted editorial pages, then the publication of the experimental studies would be more reasonable. But the 200-page commitment from the publisher would have to be a long-term commitment and not simply a single year commitment. An important feature of the AJC at the moment I believe is that it is a purely clinical journal. It is one where every attempt is made to treat both readers and authors respectfully and to publish good clinical manuscripts as rapidly as possible. The large number of paid subscribers suggests that the present policy is working satisfactorily. Thus, for the moment the present policy will remain unless additional pages set aside for experimental studies are provided by the publisher.

The meeting was adjourned to a reception provided by the publisher.

William C. Roberts

William Clifford Roberts, MD
Editor in Chief

1. Roberts WC. Alkaline paper and preserving the record. *Am J Cardiol* 1991;68:1729–1732.
2. Roberts WC. Editorial board meeting of The American Journal of Cardiology — 5 March 1991. *Am J Cardiol* 1991;67:1033–1037.

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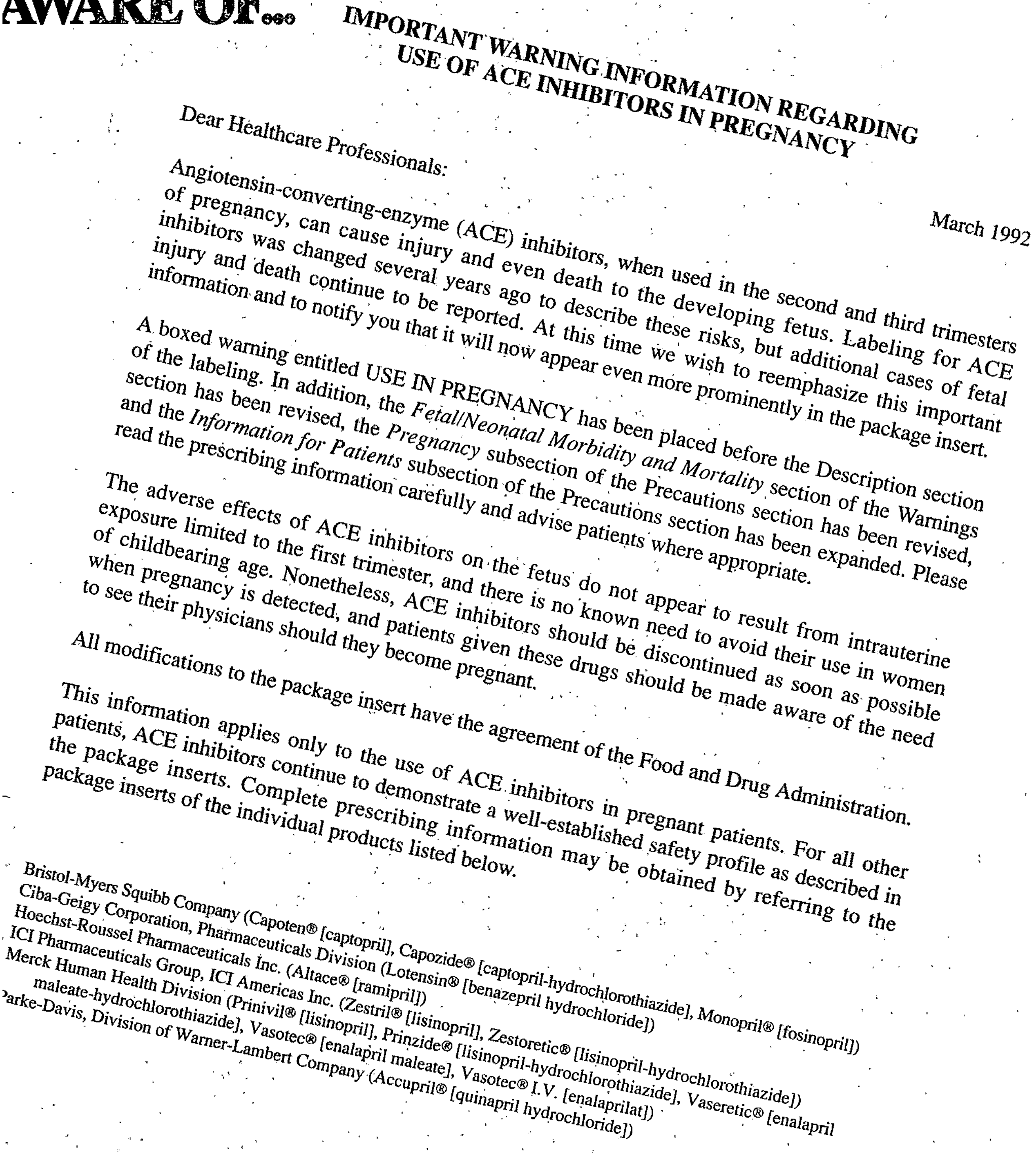

IMPORTANT WARNING INFORMATION REGARDING USE OF ACE INHIBITORS IN PREGNANCY

March 1992

Dear Healthcare Professionals:

Angiotensin-converting-enzyme (ACE) inhibitors, when used in the second and third trimesters of pregnancy, can cause injury and even death to the developing fetus. Labeling for ACE inhibitors was changed several years ago to describe these risks, but additional cases of fetal injury and death continue to be reported. At this time we wish to reemphasize this important information and to notify you that it will now appear even more prominently in the package insert.

A boxed warning entitled USE IN PREGNANCY has been placed before the Description section of the labeling. In addition, the *Fetal/Neonatal Morbidity and Mortality* section of the Warnings section has been revised, the *Pregnancy* subsection of the Precautions section has been revised, and the *Information for Patients* subsection of the Precautions section has been expanded. Please read the prescribing information carefully and advise patients where appropriate.

The adverse effects of ACE inhibitors on the fetus do not appear to result from intrauterine exposure limited to the first trimester, and there is no known need to avoid their use in women of childbearing age. Nonetheless, ACE inhibitors should be discontinued as soon as possible when pregnancy is detected, and patients given these drugs should be made aware of the need to see their physicians should they become pregnant.

All modifications to the package insert have the agreement of the Food and Drug Administration.

This information applies only to the use of ACE inhibitors in pregnant patients. For all other patients, ACE inhibitors continue to demonstrate a well-established safety profile as described in the package inserts. Complete prescribing information may be obtained by referring to the package inserts of the individual products listed below.

Bristol-Myers Squibb Company (Capoten® [captopril], Capozide® [captopril-hydrochlorothiazide], Monopril® [fosinopril])
Ciba-Geigy Corporation, Pharmaceuticals Division (Lotensin® [benazepril hydrochloride])
Hoechst-Roussel Pharmaceuticals Inc. (Altace® [ramipril])
ICI Pharmaceuticals Group, ICI Americas Inc. (Zestril® [lisinopril], Zestoretic® [lisinopril-hydrochlorothiazide])
Merck Human Health Division (Prinivil® [lisinopril], Prinzide® [lisinopril-hydrochlorothiazide], Vaseretic® [enalapril maleate-hydrochlorothiazide], Vasotec® [enalapril maleate], Vasotec® I.V. [enalaprilat])
Parke-Davis, Division of Warner-Lambert Company (Accupril® [quinapril hydrochloride])

This reminder has been sponsored by the companies listed below. For further nformation regarding ACE inhibitor products, call the manufacturer:

Bristol-Myers Squibb Company	(609) 243-6660
Ciba-Geigy Corporation, Pharmaceuticals Division	(908) 277-5049
ICI Pharmaceuticals Group, ICI Americas, Inc.	(302) 886-2231
Merck Human Health Division	(215) 661-7300

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JUNE 18, 1992

A Symposium: Advances in Echocardiography: A View Toward the Year 2000

GUEST EDITORS:

Anthony N. DeMaria, MD
Professor of Medicine
Chief, Cardiology Division
University of California, San Diego
School of Medicine
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Harvey Feigenbaum, MD
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JUNE 18, 1992 VOL. 69 NO. 20

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Professor of Medicine
Chief, Cardiology Division
University of California, San Diego
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San Diego, California

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Introduction

Anthony N. DeMaria, MD, Harvey Feigenbaum, MD

Cardiac ultrasound is a rapidly expanding diagnostic modality that promises to have greater applications in clinical cardiology in the future. In an attempt to forecast the directions in which echocardiography will evolve in the next decade, a group of experts convened for a 2-day colloquium in Williamsburg, Virginia. Brief overview presentations were followed by extensive panel discussions in which the opportunities and obstacles to future developments in cardiac ultrasound were discussed. The highlights of the colloquium are presented in this symposium. We believe that echocardiography will continue to be an exciting area of rapid technological breakthrough in the future and that many of the potential applications of cardiac ultrasound discussed in this symposium will become a reality by the year 2000.

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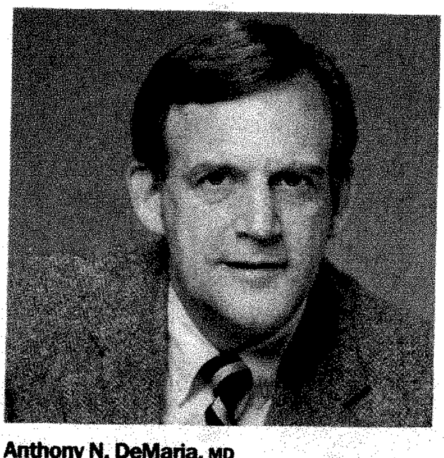

Anthony N. DeMaria, MD

Harvey Feigenbaum, MD

Future Developments in Cardiac Ultrasound: Possibilities and Challenges

Anthony N. DeMaria, MD

Several years ago I was asked to give a lecture at the annual meeting of the American Heart Association about future developments in cardiac imaging. Table I outlines the transition in cardiac imaging that had been in progress since 1970 and that I believed would be largely completed by the year 2000. In 1970 virtually all cardiac imaging required invasive techniques. By 2000, all cardiac imaging will likely be noninvasive for diagnostic purposes, although not for therapeutic purposes. Ionizing radiation was the primary imaging modality in 1970. Obviously, ultrasound and magnetic resonance imaging (MRI) have and will continue to replace radiation for many purposes in the future, and other nonradiographic techniques may be developed. Physicians dealt almost entirely with silhouette or projection images in 1970. By the year 2000, they will deal almost exclusively with tomographic images, even if computerized and reconstructed into 3 dimensions. In 1970 all images were acquired and processed in analog format. It is hoped that by the year 2000 imaging will be entirely digital. Finally, in 1970 the information content available was almost entirely anatomic. Imaging conveyed such information as whether structures were big or small, round or square, but we obtained little functional information. Increasingly, by the year 2000 we will expect and receive functional information from the images.

Currently, I believe that cardiac ultrasound can be divided into techniques that have an established role, those that are of proven value but for which the exact indications and applications are uncertain, and those that are primarily investigational. At the moment, certain aspects of cardiac ultrasound are established, such as standard 2-dimensional imaging and spectral and color-flow Doppler. There are several areas of ultrasound that are clearly of value but for which applications are still emerging, such as stress echocardiography and transesophageal echocardiography (TEE). We clearly know that these procedures are effective; the question is what their role is in specific disorders and relative to other technologies. A variety of ultrasound techniques exist that have not yet been fully developed and for which accuracy, efficacy, and optimal utilization are not yet clearly defined. Among these procedures are contrast echocardiography, ultrasound tissue characterization, intravascular ultrasound (IVUS), and even therapeutic ultrasound. I think that these developing areas will receive a large measure of our attention for the next several years. Finally, therapeutic ultrasound and nonradiographic catheterization are technologies that are in their infancy. In fact, ultrasound emitters have been placed on catheters to locate and guide catheterization without x-ray.

It is of importance to recognize that ultrasound is not the only cardiac imaging modality that is being developed or refined. At present, ultrasound is the most prominent, and certainly the most convenient and the most usable, of the cardiac imaging modalities. Indeed, echocardiography is one of the most rapidly increasing cardiac procedures from the standpoint of volume and cost. However, a number of additional noninvasive cardiac imaging modalities exist that can provide information comparable to that of echocardiography. Magnetic resonance imaging, positron emission tomography (PET), cine computed tomography (CT), and digital angiography are all techniques that are being applied clinically. So the one aspect that needs important consideration in regard to the

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future of cardiac ultrasound is what the role of echocardiography will be relative to other technologies.

There are certain issues regarding cardiac ultrasound that are generic and pertinent to all clinical applications and that need to be discussed. Foremost among these is the need and potential for getting higher quality images. Clearly, the breadth and accuracy of clinical applications of echocardiography would be increased by enhanced sensitivity and resolution. Improvements in image quality are progressively being achieved in small increments. It has been suggested that it might be possible to employ nondefracting ultrasound, and theoretically, nondefracting ultrasound could result in substantial improvement in ultrasonic images. Clearly, the ability to derive diagnostic information from ultrasound hinges on the ability to identify cardiovascular structural components accurately.

Another generic issue of fundamental importance is quantitation. In my view, the failure to derive and report quantitative measures is a longstanding embarrassment to echocardiography. Despite every attempt that has been made over the years to try to introduce standard quantitation, the majority of echocardiography reports continue to consist primarily of qualitative observations. Compared with angiography and radionuclide techniques, that is a major dilemma that must be overcome in the future. Otherwise, all ultrasonic data will be relative only to the person who does the interpretation. Improved image quality, along with digital techniques and automated border detection, may provide an answer to the need for quantitation in the future.

Digital imaging has only recently been introduced into cardiac ultrasound. Relative to other techniques, echocardiography is in the dark ages in using videotape, which is entirely analog. Videotape has only serial (rather than random) access, is a poor medium for storage, and results in image degradation. Of greater significance, once the image is recorded on videotape, it is immutable and cannot undergo postprocessing. On the other hand, images recorded in digital format can be transmitted and reproduced without degradation, can be postprocessed, and can be displayed for continuous analysis of a closed loop or side-by-side comparison of serial studies. Digital images are also well suited to quantitation.

TABLE I Evolution of Cardiac Imaging

1970	2000
Invasive	Noninvasive
Ionizing radiation	No ionizing radiation
Silhouette	Tomographic
2-dimensional	3-dimensional
Analog	Digital
Anatomic	Functional

IMAGING MODALITIES

Intravascular ultrasound: Perhaps the most exciting new development in echocardiography is IVUS.[1,2] For the first time, we have the ability to visualize the wall of a coronary artery as well as the lumen. IVUS was initially conceived as a method to guide and assess the results of various types of catheter revascularization. The potential exists for that application, as well as for sizing shunts and valvular disease, although this may be best done by intracardiac echocardiography. However, I believe that the greatest value of intravascular ultrasound is in the study of the biology of atherosclerosis.

IVUS conveys the ability to identify intramural disease that may not be visible by angiography.[3] IVUS also enables us to study the process of vascular remodeling in response to atherosclerosis. The advent of IVUS has in some ways reemphasized the limitations of angiography. It offers precision for quantitating stenoses and provides the potential to characterize plaques in terms of lipid-laden or fibrocalcific. It is reasonable to assume that the properties of plaques defined by IVUS will be related to the propensity of disruption and thrombosis, suitability for angioplasty, and likelihood of restenosis. At the moment, none of these aforementioned capabilities has demonstrated therapeutic significance, and one is not likely to make a therapeutic decision on the basis of IVUS findings. Therefore, I think that the biggest challenge will be to demonstrate the value of IVUS, not just in the patient who is undergoing percutaneous transluminal coronary angioplasty (PTCA) or some catheter revascularization, but in patients who are undergoing diagnostic angiography in general.

Clearly, IVUS will be improved in the future. There will be improved instrumentation and smaller, more flexible catheter probes. IVUS will be combined with revascularization catheters and with Doppler imaging to give on-line, real-time estimates of coronary blood flow.[4] The potential development of a forward-looking imaging probe would be the best advance possible, since it would no longer require straddling the atheroma in order to obtain an image. Forward-looking imaging catheter probes will be very difficult to develop, however, since IVUS employs transducers operating at 20–40 mHz. Sensitivity problems already exist with IVUS, and nonorthogonal orientation will compound this difficulty.

Transesophageal echocardiography: In terms of TEE, most advances will be directed to overcome the constraints of the esophagus. If TEE probes could be miniaturized, the technique would find increased application. I can foresee utilizing a miniaturized TEE probe for continuous monitoring in the coronary care unit postoperatively, and perhaps for stress echocardiography. A device already exists that attempts to do 3-dimensional reconstruction (echo CT) by the transesophageal mode. At the moment, TEE may be the technique that has the best opportunity for coronary artery visualization.

Contrast echocardiography: Contrast echocardiography has existed for many years and continues to offer the promise of a huge potential.[5] Future progress will surely be related to the development of contrast agents. Sonicated human serum albumin and certain saccharide agents have proven to be of value for quantitation and left heart imaging. The perfluorocarbons have been used for infarct imaging. Liposomes are agents that can potentially be very exciting. Thus, the transfer of contrast echocardiography from the laboratory to the clinic will likely rest on the development of suitable contrast agents.

Pulmonary transmission of contrast media has now been achieved for imaging of the left atrium and ventricle.[6] However, we cannot yet image myocardium by injection of intravenous contrast agents and therefore this remains an enormous challenge. In terms of myocardial perfusion, intracoronary and intra-aortic contrast administration can be used to visualize regional defects and coronary collaterals. However, what is really needed is the ability to measure blood flow and flow reserve.

Finally, for the year 2000, one might hope to revive attempts to determine cardiovascular pressures by the old resonating bubble technique. As with other aspects of cardiac ultrasound, contrast echocardiography will be of greatest value if it is quantitative.

Stress echocardiography: In regard to stress echocardiography, I believe that the biggest issue that needs to be addressed is the variability of application from laboratory to laboratory. It appears that some laboratories perform as many as 10 stress echocardiographic examinations each day, whereas others perform 1 per month. This variability is particularly true among the intellectual leaders in echocardiography, those in academic laboratories. Somehow, a consensus needs to be forged among echocardiographic "luminaries" as to the real accuracy and value of stress echocardiography in order for it to become the predominant stress-testing modality.

An exciting development in the area of stress echocardiography relates to the use of *nonexertional stress*. Nonexertional "stress" of the cardiovascular system has been elicited by a variety of pharmacologic agents, which have been administered in conjunction with echocardiography to detect the presence, location, and extent of myocardial ischemia. Currently, the greatest experience has been accumulated with dipyridamole and dobutamine.[7] Pharmacologic stress has been critical for patients who are unable to exercise and facilitates high-quality imaging in nearly all patients. Most recently, dobutamine stress echocardiography has been utilized to distinguish viable from necrosed myocardium.[8]

TISSUE CHARACTERIZATION

In terms of tissue characterization, it has been clear that the visual appearance of myocardium infiltrated by material such as amyloid was often abnormal by gross inspection of echocardiographic recordings. However, the subtle alterations in the acoustic properties of myocardium induced by disease processes have proven extremely difficult to detect objectively by ultrasound. Most recently, a sustained effort by investigators at Washington University in St. Louis has led to examining the cardiac cycle for variations of the integrated backscatter signal coming from the myocardium for tissue characterization.[9] It has been demonstrated that the normal cyclic variation of backscatter, a decrease in systole, is diminished in a variety of disease states, including infarction, hypertrophy, and transplant rejection. This methodology has also formed the basis for an approach to automated border detection, which should be of value in deriving quantitative data from echocardiography.

I believe that tissue characterization by cardiac ultrasound is on the threshold of providing us with information that we have not had available previously from this or any other technique, and this should be one of the great advances in echocardiography in the next few years. However, widespread application of ultrasound tissue characterization will require greater implementation of commercial equipment and a firm definition of the findings observed in specific disease states. I also think that the "tissue signature" derived from intravascular ultrasound is an important avenue to explore. To my way of thinking, we may get more information from tissue characterization of atheromas than perhaps even of the myocardium.

THREE-DIMENSIONAL RECONSTRUCTION

Three-dimensional reconstruction of echocardiograms can be of value in a variety of ways.[10] Three-dimensional orientation in echocardiography can be used to guide the examination, and know the precise path of the interrogating beam. The knowledge of the beam location in 3 dimensions should render data more reproducible and more quantifiable. Three-dimensional echocardiography can orient anatomic structures such as the mitral annulus and, even in the setting of regional wall motion abnormalities, confer the ability to measure cardiac volumes and mass accurately. Three-dimensional images may also be combined with endocardial surface area determinations; previous data have suggested that endocardial surface area determinations represent a potential modality by which regional dysfunction can be assessed, independent of translation and rotation and all the other variables of cardiac motion.

SOCIOECONOMIC CONSIDERATIONS

In any discussion of the future of cardiac ultrasound it seems appropriate to discuss finances, since in the future echocardiography may be influenced as much by socioeconomic factors as by scientific developments. There was an increase of nearly 50% in Medicare Part B expenditures (for diagnostic services) between 1980 and 1987. Of course, diagnostic services are only an intermediary step in the healing process. Nevertheless, diagnostic testing was by far the largest increase in Medicare spending during this period of time. Therefore, the cost-effective use of echocardiography must be an important consideration as we approach the year 2000. We must define which patients should undergo echocardiography, and at which stage of their disease. In addition, we should consider who should perform echocardiography, and what constitutes adequate training. Anesthesiologists and emergency room physicians are beginning to do echocardiography. It will be necessary to decide what training is required, and how an individual gets trained to deliver these services.

In the development of new echocardiographic techniques, I believe it will be critical to avoid redundant information. Cardiac ultrasound does not require better techniques to determine whether the ventricle is dilated or nondilated, or to know whether or not a myxoma is present. Echocardiography can already do that very well with existing instrumentation. What is needed are better methods to assess coronary blood flow or blood flow reserve, and myocardial viability. A technique that enables us to quantitate pericardial effusion to the nearest milliliter will not be nearly as valuable as a method to assess myocardial viability, or to characterize tissue, or to examine myocardial metabolism.

We are currently in an era of both major scientific advances in cardiac ultrasound and substantial change in the socioeconomics of medicine. Health policy will increasingly be budget driven, so that the adoption of new technology will depend on available resources. I believe that the standards and credentials for performing echocardiography are going to be increased. I believe that there will be increasing emphasis on decision making. If there is no possible finding on an echocardiogram that will lead the clinician to do something diagnostically or therapeutically to a patient, it is possible that physicians may not be reimbursed for that study. So new technology must be balanced with available resources if echocardiography is to continue to flourish.

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Intravascular Ultrasound and Intracardiac Echocardiography: Concepts for the Future

Natesa G. Pandian, MD, and Tsui-Lieh Hsu, MD

Intravascular ultrasound imaging is a catheter-based method that has been shown to be better than contrast angiography in the detailed assessment of coronary and peripheral arterial atherosclerotic lesions, arterial dissections and clots, aortic and pulmonary arterial disorders, and the effects and complications of interventional therapy in various vascular beds. Evaluation of refined ultrasound catheters, combined imaging and therapeutic devices, and off-line 3-dimensional reconstruction capabilities indicates that intravascular ultrasound could provide guidance during various catheter-based therapeutic procedures. Early experience with intracardiac echocardiography suggests that this technique could evolve as a clinically useful method with diagnostic, monitoring, and guidance applications. Future directions for further development include designing of miniaturized imaging devices, "look-forward" imaging devices, low frequency devices for whole heart imaging, multifrequency ultrasound catheters and multifunction ultrasound consoles, and approaches to real-time 3-dimensional imaging, on-line tissue characterization, automated acoustic quantification and tissue characterization, the study of myocardial perfusion, and catheter-based acoustic myocardial biopsy. These developments could lead to the conversion of catheterization laboratories into integrated imaging, monitoring, and therapeutic stations. In addition, continuous monitoring of cardiac function could be possible in the critical care unit and in the operating room as well. Ongoing advances in catheter technology and image processing indicate that these concepts are within the realm of becoming reality.

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Intravascular ultrasound imaging, a newly evolving catheter-based imaging method that has the unique capability to display cross-sectional images of vascular and cardiac structures, has captured the interest of a broad section of the cardiology community from clinical cardiologists to basic scientists. Although the concept of catheter-based ultrasound imaging is an old one, only recently has it become possible to translate the idea into a clinically useful tool.[1] The last 4 years have seen developments in this area, proceeding from prototype devices to commercially available instruments approved for clinical application. For years, selective contrast cineangiography has been the traditional method of examining blood vessels such as coronary arteries. Angiography provides a "roadmap" of the arterial tree and delineates lesions that compromise the lumen of a vessel. Arteriography has been shown to have limitations in accuracy in quantifying lesion severity, however, and it does not yield any information on the morphology of the vessel wall or the atheromatous plaques. Despite its well-known limitations, this method continues to be clinically employed because of the dearth of any other technique that can provide a greater amount of information. The availability of intravascular ultrasound (IVUS) catheters equipped with high-frequency ultrasound crystals permits in vivo visualization of the arterial anatomy in cross-section, similar to that of pathology sections.[2-7] Early human experience with this technique has provided encouraging results in terms of its clinical potential. This article will briefly review the current developments and present some ideas and concepts for future directions for this exciting area.

CURRENTLY AVAILABLE INTRAVASCULAR ULTRASOUND INSTRUMENTATION

Catheters bearing miniaturized ultrasound crystals that are interfaced to ultrasound imaging consoles constitute the IVUS instrumentation.[8-19] For examining the coronary and peripheral arteries, catheters 3.5–9 French (F) in size, carrying

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20–35 MHz frequency transducers, are used, whereas 6–10 F catheters carrying 10, 12.5, 15, or 20 MHz transducers are used for intracardiac echocardiography (ICE). Higher frequency catheters yield fine resolution images up to a small distance of about 5 mm radius; low frequency catheters have relatively greater depths of field for imaging but the resolution is less than that of 20–30 MHz devices. Currently available intravascular instruments belong to either a mechanical category or a synthetic aperture array category.

There are several designs of mechanical systems. One design has a small piezoelectric ultrasound element with a frequency of either 12.5, 20, or 30 MHz affixed to the tip of a drive shaft (probe core), which in turn is encased within a catheter. The drive shaft is connected externally to a motor that rotates the assembly of the drive shaft and the transducer at its tip at 900 rpm.[19] The processed ultrasound signals are displayed as a circular videoscan on a monitor. Other types in the mechanical category include instruments that use a deflecting mirror. In one type, the transducer element is fixed and the ultrasound energy is deflected by a rotating mirror.[3] This system employs transducer frequencies of 10–30 MHz. In another type, the mirror has a fixed position and the transducer is rotated by the motor,[11] at rotational speeds of 1,500–1,800 rpm. All the abovementioned devices use a single element transducer, require filling the catheter tip with fluid, and are rotated by a small external motor.

An electronic array concept using multiple transducer elements is employed in the second category of IVUS devices. One such instrument uses up to 64 elements operating at a frequency of 20 MHz.[5,6] The ultrasound elements are electronically activated in sequence to produce a 2-dimensional image. Catheters of 3.5–7.8 F size are available for use with the multielement system. Because there are no rotating components, the central lumen of the catheter can be used for guidewires or for fluid injection.

INTRAVASCULAR ULTRASOUND AND INTRACARDIAC ECHOCARDIOGRAPHY: DEMONSTRATED CAPABILITIES

Coronary and peripheral arterial circulation: Many in vitro investigations correlating IVUS images of arterial segments to gross anatomic and histologic sections have shown that IVUS images (1) faithfully display the arterial anatomy, (2) depict atheromatous plaques, (3) allow identification of the gross composition of an atheromatous plaque (predominantly calcific, fibrous, or fatty), (4) permit recognition of complex lesions, (5) demonstrate the presence of dissection and intimal flaps and clots, (6) aid in the recognition of the effects and complications of angioplasty, and (7) allow for reliable quantitation of the arterial lumen size, wall thickness, plaque thickness, and arterial stenosis (Table I).[9–15] In addition, the accuracy of quantitative data derived from 3-dimensional reconstructions has been verified by ultrasound–anatomic correlations.[16,17] Based on these foundations, in vivo studies carried out in animals and humans have documented the ease of IVUS imaging of coronary and peripheral circulation, as well as its safety. Despite its use in a large number of patients, no complications have been documented except for a few cases of transient coronary spasm, without any sequelae.[11–23]

TABLE I Demonstrated Capabilities of Intravascular Ultrasound and Intracardiac Echocardiography

Intravascular ultrasound:

Is easy to perform and is safe
Yields detailed images of coronary and peripheral arterial anatomy
Depicts atheromatous plaques and allows for assessment of the composition of the plaque
Permits recognition of complex arterial lesions
Allows for reliable quantitation of arterial lumen size, wall thickness, plaque thickness, and arterial stenosis
Identifies atheromatous disease in angiographically normal arterial segments
Is a good technique for identification of left main coronary stenosis
Demonstrates the presence of dissection, intimal flaps, and intra-arterial clots
Aids in the recognition of the effects and complications of balloon angioplasty and atherectomy
Allows 3-dimensional reconstruction immediately after imaging
Aids in the recognition of aortic atherosclerosis
Useful in the evaluation of aortic dissection
Aids in the delineating aortic coarctation and assessing the effects of balloon dilation
Can be introduced into the pulmonary arteries safely
Displays the structural changes in the pulmonary arteries in patients with pulmonary hypertension
Intracardiac echocardiography can be safely performed and cardiac structures visualized

Clinical experience with IVUS imaging of coronary arteries indicates that this technique provides excellent information on arterial anatomy, much more than what one can understand by looking at the silhouette image obtained with angiography.[6,11–23] Compared with angiography, IVUS imaging appears to have the following strengths: (1) identification of atheromatous disease in vessel segments that appear normal on angiograms (Figure 1); (2) unmasking of left main coronary artery lesions unappreciated on angiography; (3) delineation of the circumferential extent of the atheroma, the true absolute cross-sectional area of the lumen, and the changes that have evolved in the arterial wall secondary to atherosclerosis; (4) recognition of whether an atheromatous lesion is predominantly soft, fibrous, or calcified; (5) detection of dissections and intimal tears following balloon angioplasty that are not seen on angiograms (Figure 2); and (6) appreciation of the effects of mechanical atherectomy.[24] Although IVUS imaging has been found to have the abovementioned capabilities, one area that has not been well addressed is the ability to discriminate a thrombus from a soft atheroma, since the clinical experience in patients with thrombotic occlusions is limited. Early results from studies in patients with peripheral arterial disease demonstrate that IVUS imaging has similar strengths and potential in the peripheral circulation as well. Systematic investigations are currently in progress addressing the following unresolved hypotheses: (1) The appearance of atheromatous lesions on IVUS images is helpful in stratifying the patient for appropriate management (medical therapy, catheter-based intervention, or surgery); (2) IVUS categorization of atheromatous lesions is useful in choosing the correct interventional procedure or the correct combination of interventional procedures; (3) IVUS imaging after interventional procedures can identify complications that warrant immediate action in the interventional laboratory; (4) IVUS imaging of an atheromatous lesion before or after an intervention can identify lesions at a high risk of restenosis; and (5) recognition of atheromatous disease by IVUS imaging in angiographically normal vessels has prognostic and therapeutic implications.

Aorta and pulmonary arteries: Ultrasound catheters have also been found to be useful in evaluation of disorders involving the aorta and pulmonary arteries. Clinical studies have indicated that IVUS imaging of the aorta can depict atherosclerotic disease of the aorta, acute aortic dissection, and aortic coarctation.[25,26] Atherosclerotic disease of the aorta and its major branches presents a similar spectrum of abnormalities on IVUS images as seen in other vessels. In patients with aortic dissection, the presence, location, and extent of aortic dissection, branch involvement, and the contents of the true and false lumens can be identified by IVUS imaging. Although IVUS imaging cannot be considered superior to other diagnostic techniques such as transesophageal echocardiography, aortography, or computed tomography, it appears that it can offer similar information without requiring contrast medium and can be employed quickly in the catheterization laboratory to exclude aortic dissection. When used in patients with aortic coarctation, catheter ultrasound has permitted evaluation of the site of coarctation, the size of the prestenotic, stenotic, and poststenotic sites, the morphologic severity of coarctation, and the effects and complications of balloon dilation. It is very likely that IVUS imaging could become a necessary adjunct to angiography in the performance of balloon dilation of aortic coarctation.

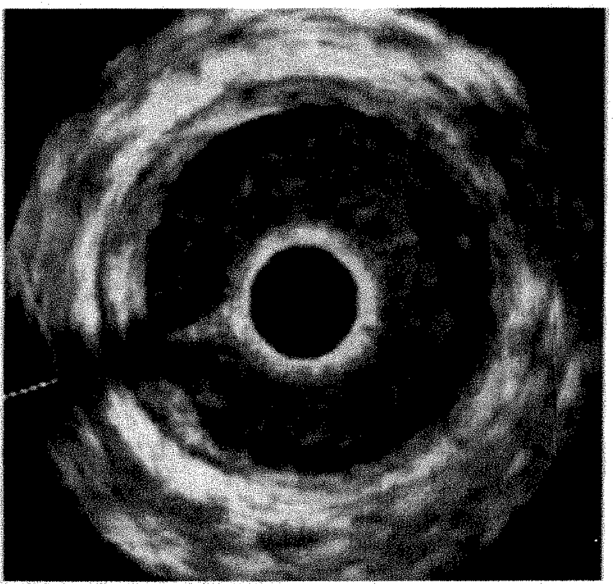

FIGURE 1. Intravascular ultrasound image of an iliac artery with a curvilinear atheromatous plaque (7 to 1 o'clock) in an angiographically normal segment. The ultrasound catheter signal is seen in the center of the lumen. The adjacent discrete signal is the guide wire signal.

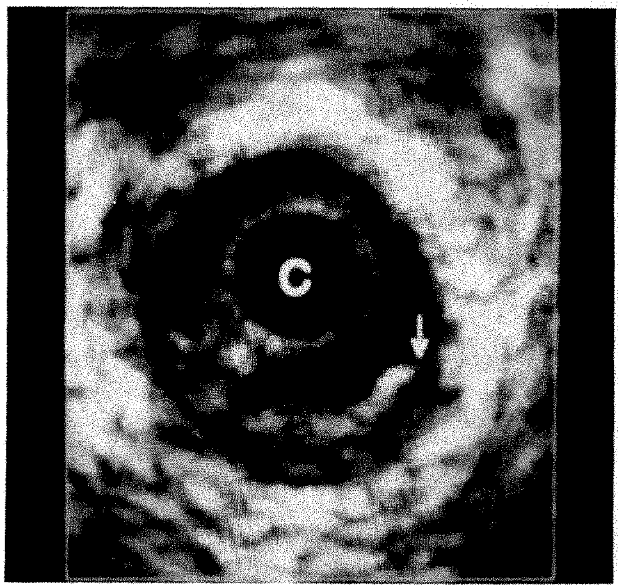

FIGURE 2. Intravascular ultrasound image of the proximal portion of left anterior descending coronary artery in a patient immediately after balloon angioplasty. The arrow points to a site of dissection caused by the dilation procedure.

Ultrasound catheters can be safely passed into the pulmonary arteries, either with the use of a guide wire or via a long sheath placed in the pulmonary artery.[27] Current clinical experience in patients with pulmonary hypertension has demonstrated that IVUS imaging can display the structural changes in distal pulmonary arteries and may also permit the study of the vasomotor function and the mechanical properties of pulmonary arteries. Diminished pulsatility has been observed in diseased vessels, and decreased vascular reactivity to agents such as nitroglycerin and nitroprusside has been demonstrated in patients with cardiomyopathy and pulmonary hypertension.[28] This technique may be helpful in investigations of the pathophysiology of pulmonary arterial dysfunction in patients with heart failure and allow for the assessment of the reversibility or irreversibility of pulmonary hypertension. Work correlating ultrasound images with histologic analysis is currently in progress and is likely to provide a basis for ultrasound categorizations of the structural abnormalities in patients with pulmonary vascular disease.[29] Besides its potential application in pulmonary hypertension, IVUS may become useful in the evaluation of other pulmonary arterial diseases such as peripheral pulmonary arterial stenosis.

Intracardiac echocardiography: Ultrasound catheters can be advanced into various cardiac chambers and the cardiac structures visualized in real-time from within the heart. The impetus behind the attempts to develop the modality of ICE is predominantly related to the need for better guidance during various catheter-based therapeutic procedures for treating cardiovascular lesions.[30] Difficulties in the performance of the procedure and a considerable number of complications continue to be encountered when only fluoroscopy and intermittent contrast angiography are employed as primary guidance modalities during balloon valvuloplasty to treat valvular stenosis, occluder placement for shunt lesions, and catheter ablation of conduction tissues, accessory pathways, and arrhythmogenic foci. With the notion that ICE with ultrasound catheters could evolve as a useful guidance modality, catheters equipped with 20 MHz transducer elements have been used to image cardiac structures.[31,32] Catheters with 20 MHz transducers yield high-resolution images of chamber walls, the interatrial septum, ostium of the coronary sinus, and portions of the valve structures. Intracardiac ultrasound imaging in children with pulmonic stenosis has yielded images of stenotic pulmonic valves before and after balloon dilation. Atrial septal defects, masses attached to the atrial septum and pericardial effusion have been diagnosed with 20 MHz ICE catheters.[33,34]

Although 20 MHz ultrasound catheters have provided high-resolution images of cardiac structures when placed adjacent to the region of interest, the limited depth of field associated with such a high-frequency transducer has precluded visualization of larger portions of the heart, particularly in adults. Cardiac chambers cannot be adequately visualized and hence imaging with these catheters is inadequate to provide guidance for interventional procedures and in monitoring ventricular function. To overcome this drawback, catheters with lower frequency transducers capable of providing relatively greater depth of field for imaging were fabricated. Ultrasound catheters with a transducer frequency of 12.5 MHz are currently available for intracardiac imaging.[35–38] By allowing an imaging depth up to 2 cm radius from the catheter tip, these catheters provide the ability to visualize cardiac structures of larger dimension. Aortic and pulmonic valves are visualized in their entirety and greater portions of the tricuspid and mitral valves are seen. Retrograde catheterization is currently required for better imaging of the left side of the heart. Image processing with the currently available instrumentation has not kept pace with the decreasing frequency of the ultrasound catheters, and hence the advantage of low frequency catheters has not been fully realized. With optimized image processing, these 12.5 MHz instruments are likely to make a truly greater imaging depth available for use.

EVOLVING DEVELOPMENTS

Coronary and peripheral arterial circulation: One important development has been the availability of smaller sized ultrasound catheters for use in the coronary circulation. Although catheters of 4–5 F can be employed to examine proximal coronary arteries, they are too big to be advanced into the distal vessels or across stenotic areas. Catheters <4 F in size are becoming available, and this development is likely to facilitate their use.[39] Also, the incorporation of higher frequency ultrasound transducers (30–35 MHz) in the coronary catheters appears to yield higher resolution images of the vessels. Advances in catheter technology have led to the development of prototype combination devices that incorporate ultrasound transducers within therapeutic devices such as balloon angioplasty and atherectomy catheters.[40] Such instruments

TABLE II Promising Early Results of Intravascular Ultrasound and Intracardiac Echocardiography but Need Further Experience

- Smaller sized ultrasound catheters (< 4F) permit visualization of distal vessels.
- Higher frequency (30 to 35 MHz) catheters allow for better delineation of coronary anatomy.
- Intravascular ultrasound appearance of atheromatous lesions is helpful in choosing the specific therapeutic approach.
- Intravascular ultrasound imaging is helpful in directly guiding the performance of interventional procedures such as angioplasty, atherectomy, and stent placement.
- Intravascular ultrasound characterization of the effects and complications following interventional procedures is helpful in immediate decision-making regarding further intervention.
- Intravascular ultrasound aids in the identification of angiographically silent coronary disease in patients who have had heart transplantation.
- Combination devices (imaging and balloon angioplasty; imaging and atherectomy) aid in the performance of interventional procedures.
- Devices that combine imaging and Doppler modalities are useful in the simultaneous assessment of anatomic and hemodynamic severity of coronary stenosis.
- Intravascular ultrasound is useful in the study of arterial vasomotion.
- Intraoperative intravascular ultrasound imaging of coronary arteries yields useful information.
- Intravascular ultrasound imaging of pulmonary arteries in patients with pulmonary hypertension may aid in assessing the state of reversibility of pulmonary hypertension.
- Intravascular ultrasound can depict embolic material in pulmonary arteries in pulmonary embolism.
- Low-frequency ultrasound catheters (12.5 and 10 MHz) provide increased depth of imaging field and allow for the visualization of larger portions of the heart by intracardiac echocardiography.
- Balloon-tipped, flow-directed ultrasound catheters allow intracardiac echocardiography without fluoroscopy.

should make it possible to visualize the actual dilation or plaque removal procedure and to guide the performance of such procedures. The avoidance of unnecessary catheter exchanges is an added and important advantage of combined imaging and therapeutic devices (Table II).

Initial experience in patients who undergo stent placement in the coronary and peripheral arteries indicates that IVUS imaging could aid in the appropriate placement of the stent, in identifying incomplete stent expansion or its opposition to the wall, and in demonstrating the mechanism behind restenosis in patients who have had stents placed.[41,42] Besides its use in the study of atherosclerotic coronary artery disease, IVUS imaging also is being employed in the assessment of coronary anatomy in patients who have had cardiac transplantation.[43] The type and composition of lesions that evolve in the coronary vessels of these patients are being examined in systematic studies. Work is also in progress employing computerized tissue characterization methods to understand better the ultrasound anatomy of arterial lesions.[44] Developments in this area are likely to enhance tissue identification by ultrasound and to decrease interobserver variability in the interpretation of IVUS images.

Prototype ultrasound catheter devices capable of providing flow velocity data as well as imaging information have yielded encouraging early results.[45] Attempts are also being made to develop a device that will lend itself to performing both ultrasound imaging and fiberoptic angioscopy.[46] Besides these innovations, capability to reconstruct 3-dimensional images of arterial segments is also becoming possible using off-line image processing systems. Three-dimensional depictions developed from 2-dimensional intravascular images portray the atherosclerotic lesions in a more comprehensible form and may yield a better appreciation of the effects and complications of interventional procedures.[47] Wire-sized Doppler probes yielding flow-velocity data have recently become available, and the use of this modality may further the ability to understand the hemodynamic significance of arterial obstructions.

Another area of active investigation is the study of the arterial vasomotor function. Preliminary studies have pointed to the potential of IVUS in examining the distensibility, stiffness, and vasomotor changes of peripheral and coronary arteries.[48] Attempts have also been made to utilize IVUS imaging in the operating room to image the coronary arteries and venous bypass grafts, and the feasibility of visualizing these vessels in a cardioplegic heart has been demonstrated.[49] More experience with this approach to the intraoperative visualization of the coronary arteries is likely to aid the surgeon in the performance of bypass procedures in a more optimal manner. Further work is required to define the precise role of IVUS imaging in the study of vascular pathology, physiology, and biology in a variety of clinical settings.

Aorta and pulmonary arteries: Ongoing work with the use of IVUS catheters in pulmonary circulation and aorta indicates that IVUS imaging has the potential to become an important tool in the study of disorders involving these vessels and may lead to the development of new therapeutic approaches. Experimental work with the use of combined dilation and imaging devices suggests that the performance of dilation procedures and stent placements for the treatment of aortic coarctation and peripheral pulmonary arterial stenosis may be aided by IVUS imaging. Similarly, catheter ultrasound could assist in the deployment of stents for controlling aortic dissection in selected circumstances. Experimental and early clinical studies portend to the possible role of IVUS imaging in delineating embolic material in acute pulmonary embolism and in depicting pulmonary arterial branch stenosis.[50,51] Since contrast angiography has well-known risks in patients with pulmonary vascular diseases, the ultrasound technique could play a valuable role in various disorders of the pulmonary circulation. Some preliminary studies also indicate that 3-dimensional reconstruction of pulmonary arteries is feasible.[52] Such a strength is likely to enhance the use of IVUS imaging in pulmonary arterial and aortic disorders.

Intracardiac echocardiography: There is continued progress in the area of ICE in expanding the size of the imaging field and enhancing the signal display. Prototype catheters with 10 MHz ultrasound transducers are currently being evaluated in patients (Figure 3).[53] These catheters yield imaging fields of 8 cm diameter. Initial results in patients suggest that the atrial and ventricular chambers are seen to a greater extent and that it is possible to visualize portions of the left heart structures from the right atrium and right ventricle. Experimental work also points to the potential of ICE in the assessment of left ventricular wall motion abnormalities and in the study of myocardial perfusion.[54] Further work is required to test the strength and limitations of these catheters. It is likely that these devices could be useful in selected patients, although catheters with even lower frequency transducers would be needed for consistent imaging of the left heart from the right heart in adults.

Other innovations being examined are balloon-tipped flotation ultrasound catheters that, when introduced into the right atrium, are directed into the pulmonary arteries by the force of the blood flow itself, permitting visualization of the right heart chambers and pulmonary arteries (Figure 4).[55]

CONCEPTS FOR THE FUTURE

Coronary and peripheral arterial circulation:

INSTRUMENTATION: Ongoing advances in catheter craft and image-processing technology promise further advances in IVUS imaging. Some developments that we could envision as likely to make intravascular ultrasound more versatile include: (1) Miniaturization of imaging devices: Although ultrasound catheters 3.5–4 F in size are being manufactured, further miniaturization of the devices would allow their use in examining distal vessels and crossing critically narrowed arterial segments. Guide wires with ultrasound elements that could be passed through conventional catheters into blood vessels in an atraumatic manner could be helpful in imaging any section of an artery, particularly if they could be introduced through a sideport or a central port in the catheter. (2) Refinement of combined devices: Besides the development of instruments that incorporate imaging elements within balloon, atherectomy, and laser angioplasty devices, and those that combine imaging and Doppler modalities, devices that combine ultrasound imaging within stent placement catheters could be constructed to aid in the diagnostic and therapeutic procedures. (3) "Look-forward" imaging devices: Current intravascular ultrasound instruments permit acoustic imaging in a plane that is perpendicular to the tip of the catheter and hence can provide information only at the site of the catheter tip. Fabrication of catheters with ultrasound elements mounted in a manner that would allow visualization of structures in front without significant image distortion would be of value when examining arteries with obstructive lesions. (4) On-line 3-dimensional reconstruction or real-time 3-dimensional intravascular imaging: 3-dimensional reconstructions of vascular images currently require another off-line image processing system into which the 2-dimensional images are fed for review and reconstruction. It would be more advantageous to combine the 3-dimensional capabilities to the imaging instrument itself so that 3-dimensional depictions could be displayed as intravascular imaging is performed. Such a facility would make it easier to comprehend the vascular

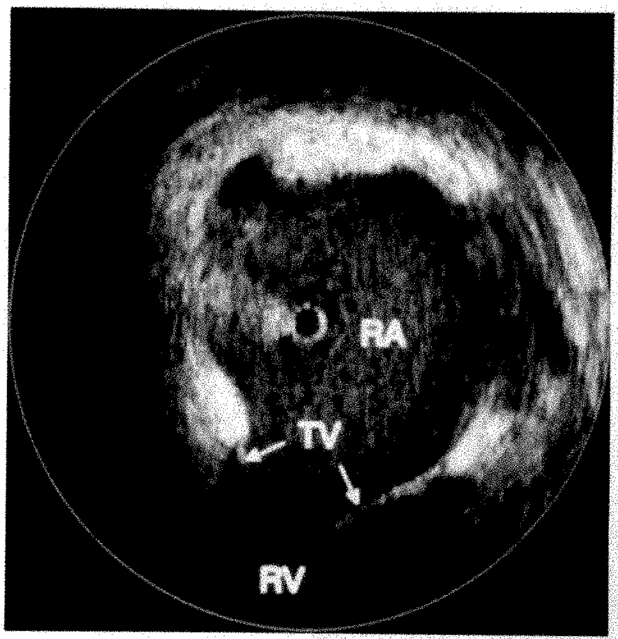

FIGURE 3. Image of the right atrium (RA) in a patient obtained with the use of a 10 MHz ultrasound catheter. RV = right ventricle; TV = tricuspid valve.

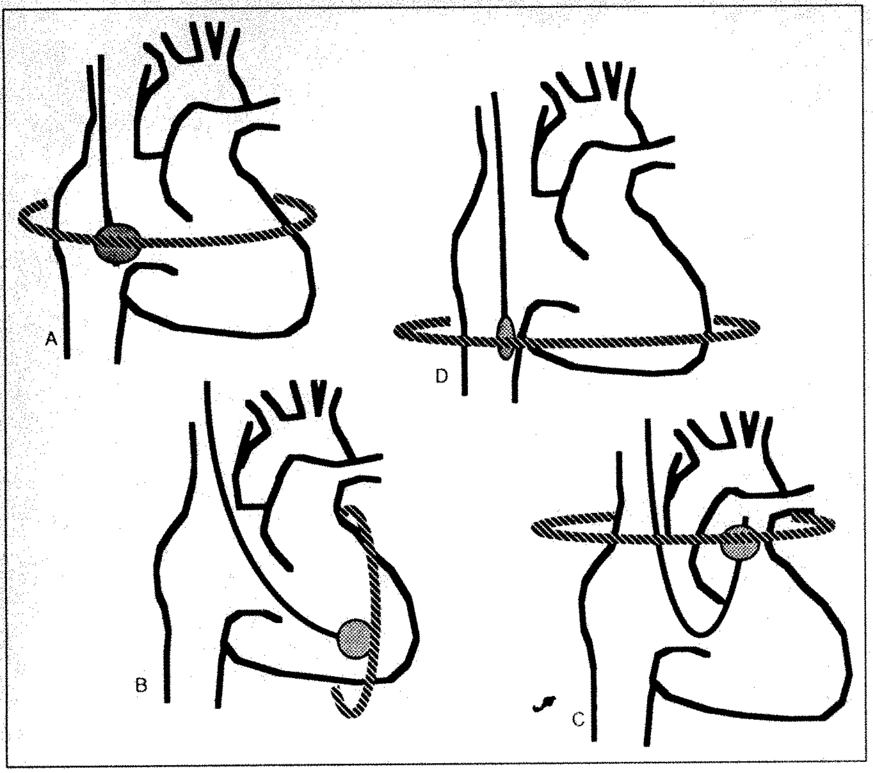

FIGURE 4. Schematic depicting the intracardiac echocardiographic imaging planes available with the use of a balloon-tipped, flow-directed ultrasound catheter. A, B, and C show the imaging planes that could be obtained as the catheter is carried through the right heart; D shows the plane available when the balloon is deflated and the catheter is advanced into the inferior vena cava.

anatomy during interventional procedures and take appropriate therapeutic steps. (5) On-line tissue characterization: Further work directed to computerized image processing and color encoding of tissues could aid in the presentation of 3-dimensional images, with abnormal tissues displayed in specific shades or colors. This would lead to a better assessment of arterial pathology. (6) Incorporation of intravascular imaging instrumentation in the catheterization laboratory equipment: At the present time, IVUS imaging requires introduction of another piece of equipment to an already crowded catheterization laboratory. The ultrasound imaging console could be easily incorporated within the angiographic instrumentation or the monitoring equipment (Figure 5). Ports or connections attached to the table could aid in the handling of the catheters. The ultrasound videomonitor can be combined with the fluoroscopic monitors to ease the near-simultaneous observation of the ultrasound images along with the electrocardiographic and hemodynamic displays. (7) Multifunction ultrasound instrument: Ultrasound imaging consoles currently used for IVUS imaging are optimized primarily for this mode of imaging. Current advances in image processing

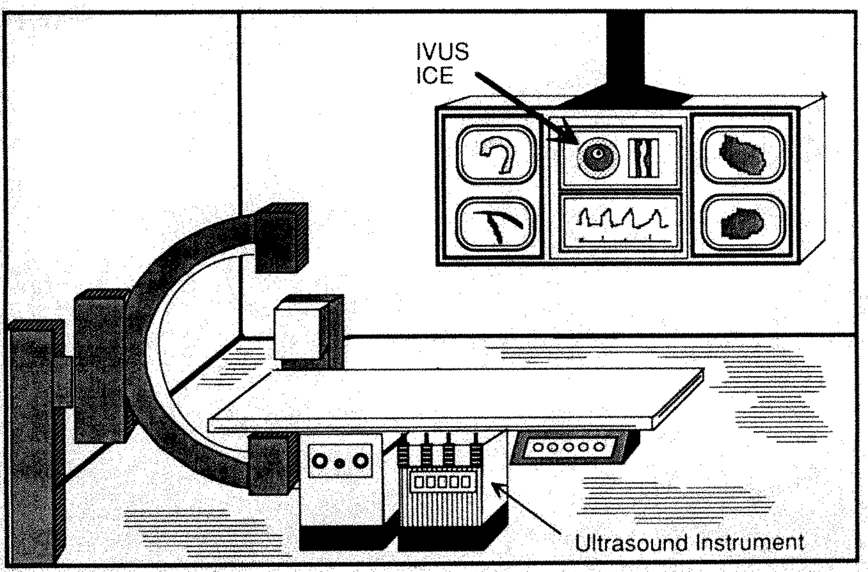

FIGURE 5. Schematic illustrating the scenario of an integrated imaging station in the invasive laboratory. ICE = intracardiac echocardiography; IVUS = intravascular ultrasound.

could be utilized to modify ultrasound instruments so that they can be interfaced with any type of ultrasound probe, from 2 MHz transthoracic echocardiographic transducers to 40 MHz ultrasound catheters (Figure 6). This would allow better utilization of the ultrasound systems and also save cost.

APPLICATIONS: The future role of IVUS is likely to be that: (1) it will become the "gold standard" in the assessment of coronary and peripheral arterial pathology; (2) it will aid and guide performance of various interventional procedures; (3) 3-dimensional intravascular ultrasound images of arteries will be the method of choice to study the progression and regression of atherosclerosis; (4) real-time IVUS images combined with pressure and flow recordings will allow for detailed studies of arterial physiology; (5) intraoperative imaging of coronary arteries, when refined, could assist the surgeon not only in choosing the optimum site for anastomosis of grafts, but also may open new approaches to the intraoperative management—e.g., besides performing bypass surgery on certain vessels, the surgeon may choose to perform intraoperative atherectomy or dilation for lesions that are not ideal for bypass or for intervention in the invasive laboratory; and (6) it will become an excellent research tool for the study of blood vessels.[56]

TABLE III Concepts for Future Development of Intravascular Ultrasound and Intracardiac Echocardiography

Intracoronary imaging
Miniaturization of imaging devices
Refinement of combination devices including stent placement catheters
"Look-forward" imaging devices
On-line or real-time 3-dimensional intravascular Imaging
On-line tissue characterization
Incorporation of intravascular imaging instrumentation in the catheterization laboratory equipment
Multifunction ultrasound instrument
Imaging of aorta and pulmonary arteries
Three-dimensional imaging capability for assessment of aortic disorders
Devices for simultaneous study of pulmonary arterial image, pressure, and flow
Combination of intravascular ultrasound element and therapeutic (dilation, retrieval, or fragmentation) devices for pulmonary arterial branch stenosis and thromboembolism
Intracardiac echocardiography
Low-frequency devices for whole heart imaging from the venous side
Multifrequency ultrasound catheters
Integrated imaging and monitoring station in the invasive laboratory
Combination intracardiac devices
Three-dimensional intracardiac echocardiography
Automated acoustic quantification of intracardiac images
Intracardiac echocardiographic assessment of myocardial perfusion
Intracardiac echocardiography without fluoroscopy
Intracardiac echocardiographic monitoring in the operating room
Continuous monitoring of cardiac function in critical care units
Monitoring of cardiac function in ambulatory patients
Catheter-based acoustic myocardial biopsy

Aorta and pulmonary arteries: Many of the above-mentioned concepts, when developed, will strengthen the use of IVUS imaging in the assessment of aortic and pulmonary arterial disorders (Table III). In particular, the following potential applications could be envisioned: (1) 3-dimensional display of aortic abnormalities such as aortic dissection and coarctation would aid in the management of these disorders in the interventional laboratory; (2) real-time IVUS images of the pulmonary arteries combined with pressure and flow data

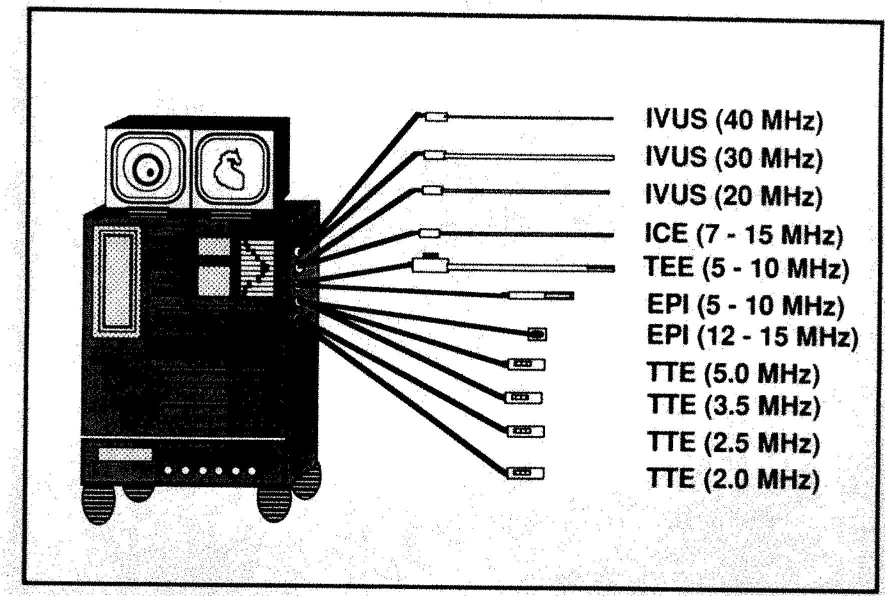

FIGURE 6. Schematic of a multifunction ultrasound system that can be interfaced with a variety of ultrasound devices for performing multiple modalities of ultrasound imaging. EPI = epicardial echocardiography; TEE = transesophageal echocardiography; TTE = transthoracic echocardiography. For other abbreviations, see Figure 5.

would lend themselves to sophisticated studies of pulmonary arterial physiology and pathophysiology; (3) IVUS imaging of pulmonary arteries in patients with pulmonary hypertension is likely to yield a better approach to the assessment and treatment of pulmonary hypertension; and (4) instruments combining IVUS with therapeutic retrieval or fragmentation devices are likely to develop newer treatment strategies for pulmonary embolism.

Intracardiac echocardiography: ICE is already evolving as a viable method with a number of potential applications. We would point out the following concepts for future developments in this area: (1) Whole heart imaging with the use of low-frequency devices: Although 12.5 and 10 MHz ultrasound catheters permit visualization of the cardiac structures, consistent visualization of all cardiac chambers from one location is still difficult. Rather than introducing the ultrasound catheters into various chambers selectively for imaging various cardiac structures, it would be preferable to perform only right heart catheterization, place the ultrasound catheter in the right-sided chambers, and then be able to visualize the entire heart from the venous side. This concept has been well described in our previous experimental studies (Figure 7).[57] For translating this into a clinical approach, catheters equipped with ultrasound transducers of 7–8 MHz would be necessary. The catheter could then be placed in the right heart in a manner similar to placing a temporary pacemaker electrode or a central venous catheter, and continuous real-time imaging of right and left ventricular function could be possible in a variety of clinical settings. ICE performed in this manner could aid in the performance of many interventional procedures and also allow for monitoring of ventricular function and for detection of complications such as cardiac perforation and tamponade, rupture of valvular structures and ventricular dysfunction. An alternative approach to the use of ultrasound catheters for performing ICE could be the use of miniaturized transesophageal echocardiography probes; these are likely to be expensive, but they could be reused if a sterile disposable sheath is employed to cover the device. Such devices would have the advantage of providing spectral and color-coded Doppler flow information as well. (2) Catheters with multifrequency ultrasound elements: If catheters with ultrasound elements that could be activated at varying frequencies are developed, they would be more versatile in facilitating the performance of high-frequency IVUS imaging of coronary arteries and low-frequency intracardiac imaging. (3) Integrated imaging station in the invasive laboratory: ICE instrumentation could be incorporated within the catheterization laboratory equipment, as suggested for IVUS imaging, so that the ease of performing and observing ICE is enhanced in the invasive laboratory (Figure 5). (4) Combination intracardiac devices: Combining ultrasound imaging elements and therapeutic devices such as balloon valvuloplasty catheters could be helpful during the performance of such treatment procedures. (5) Three-dimensional ICE: Developments used for 3-dimensional intravascular imaging can be employed to perform 3-dimensional ICE as well. From such 3-dimensional reconstructions, multiple imaging planes could be derived to examine any desired structure in greater detail with a better spatial perspective. (6) Automated border detection and quantification in ICE: The advances in automated border recognition and acoustic quantification developed for analysis of transthoracic and transesophageal echocardiograms could be

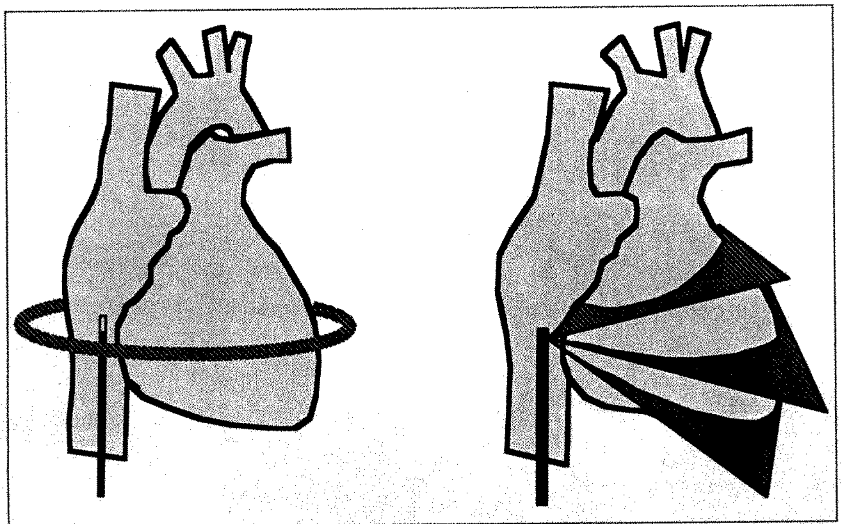

FIGURE 7. Possible intracardiac echocardiographic approaches to the imaging of the whole heart with the ultrasound device placed in the right heart. One approach could be the use of an ultrasound catheter with a frequency low enough to provide an adequate depth of field for whole-heart imaging from the right atrium or the vena cavae (*left*); Another approach could be the use of miniaturized transesophageal type of ultrasound probe advanced into the inferior vena cava or the right atrium (*right*).

coupled to intracardiac imaging as well so that both visual and quantitative information can be obtained from ICE. Such a strength would make this imaging modality a powerful monitoring tool. (7) ICE assessment of myocardial perfusion: The study of myocardial perfusion with the use of ultrasound contrast agents has been actively explored for a number of years. One of the problems hampering its development is the inconsistent quality of echocardiographic images obtained by the transthoracic approach. The increased resolution available with refined ICE instrumentation could make it easier to study myocardial perfusion by combining these techniques (Figure 8). (8) ICE outside the catheterization laboratory: The current ability to advance the ultrasound catheters in an atraumatic manner with the use of guide wires and the translation of the experimental flow-directed ultrasound catheter into a clinical device could allow one to perform intracardiac echocardiography without fluoroscopy. Such developments could lead to the use of ICE in the intensive care units, operating room, and in the echocardiography laboratory. (9) ICE in the operating room: In cases in which transesophageal echocardiography and epicardial echocardiography are impractical, ICE could potentially serve their guidance and monitoring roles. (10) Continuous monitoring of cardiac function in the critical care unit: Since ventricular function is an important determinant of the clinical course in many patients, ICE could potentially allow continuous monitoring of cardiac function in the critical care units. It is not farfetched to imagine the scenario of a cardiac care unit, with facilities for monitoring on-line intracardiac ultrasound images along with electrocardiographic and hemodynamic data (Figure 9). (11) Ambulatory monitoring of cardiac function using miniaturized intracardiac ultrasound instrumentation: Extreme miniaturization of ultrasound instrumentation could be envisioned to permit continuous monitoring of cardiac function in ambulatory patients to identify ischemic events and other transient cardiovascular dysfunction (Figure 10). (12) Catheter-based acoustic myocardial biopsy: It has been recently demonstrated that acoustic microscopy of myocardial tissue could yield diagnostic quality information at a cellular level.[58] Currently available acoustic microscopic equipment is rather large. If such instrumentation could be miniaturized, it is conceivable that

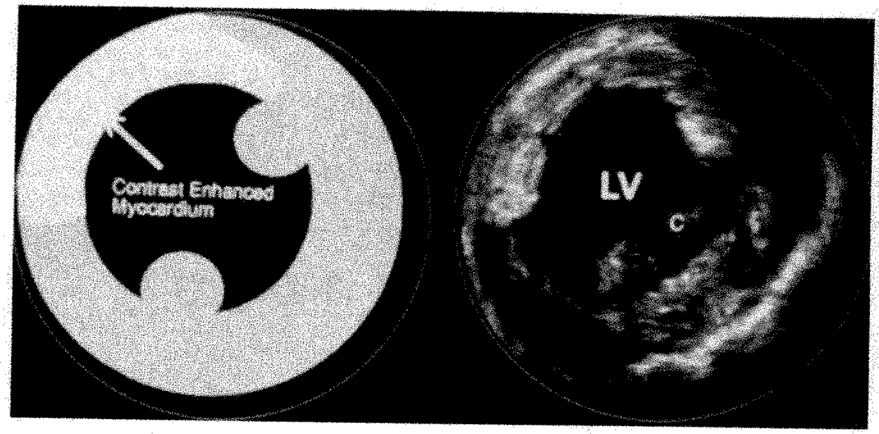

FIGURE 8. Intracardiac echocardiographic image of the left ventricle obtained in a dog after occlusion of left anterior descending coronary artery. Ultrasonic contrast medium has been injected into the artery distal to the occlusion site. The ischemic area appears thinner and the myocardial contrast enhancement in the risk area appears clearly delineated.

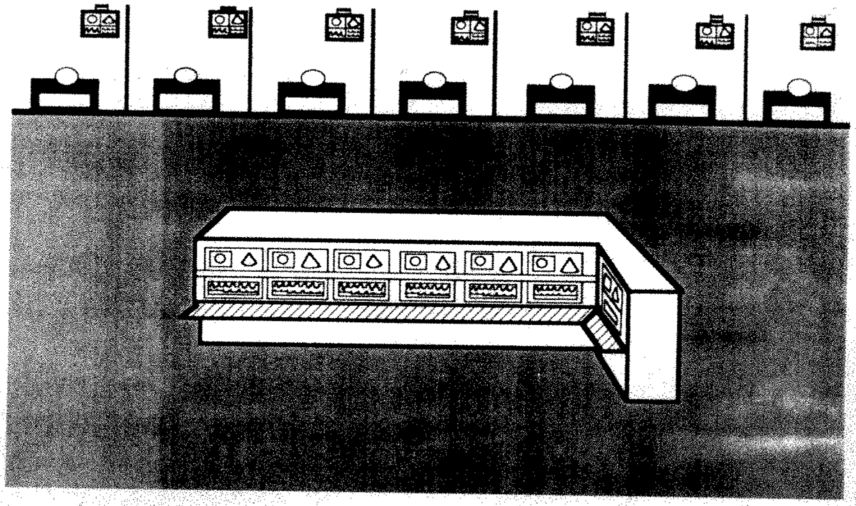

FIGURE 9. Schematic illustrating the scenario of continuous monitoring of cardiac function in a critical care unit. Along with monitoring of electrocardiogram and pressures, cardiac images could be displayed on the monitors.

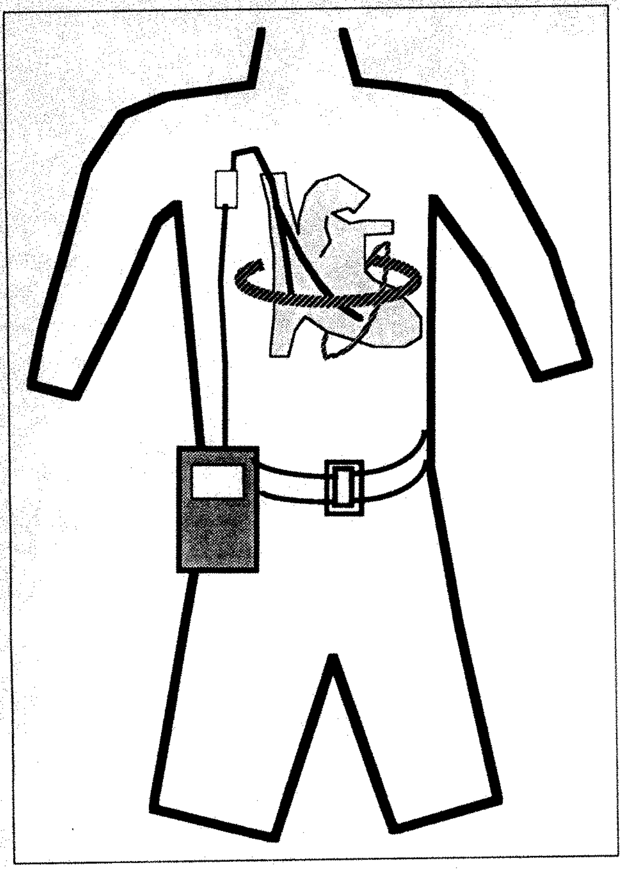

FIGURE 10. Schematic depicting the potential of a miniaturized ultrasound device allowing for monitoring of cardiac function in an ambulatory subject.

such tissue characterization studies could be performed using an intracardiac catheter bearing extremely high-frequency ultrasound elements.

CONCLUSION

Intravascular ultrasound is evolving as a unique cardiovascular imaging technique with a strong clinical potential. Current developments clearly indicate that this method is likely to play a valuable role in the management of coronary and peripheral arterial disorders. Early work in other cardiovascular disorders suggests that this technique has a promising potential in the evaluation of many other cardiovascular disorders as well. Developments in the coming years are likely to define the precise role of intravascular and intracardiac ultrasound imaging in clinical and investigative cardiology.

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Intravascular Ultrasound of the Coronary Arteries: Current Applications and Future Directions

Steven E. Nissen, MD, John C. Gurley, MD, David C. Booth, MD, and Anthony N. DeMaria, MD

Although angiography is widely applied in the diagnosis of the coronary artery disease (CAD), studies have questioned the accuracy of radiographic methods. Miniaturized intravascular ultrasound devices offer several potential advantages, including a tomographic orientation and the ability to characterize atherosclerotic plaques. Two dissimilar technical approaches to transducer design have emerged: mechanically rotated devices and multi-element arrays, each yielding small coronary catheters (1.1–1.8 mm in diameter). Initial studies of coronary ultrasound have demonstrated few serious untoward effects. In most normal subjects, the vessel wall is laminar in appearance with an intimal leading edge and subintimal sonolucent layer averaging ≤0.20 mm in thickness. In most CAD patients, the thickness of the leading-edge or sonolucent zone is abnormally increased. Atherosclerotic abnormalities are frequently evident in segments with no angiographic lesion. At sites with a circular lumen shape, minimum diameter by ultrasound and angiography correlate closely, r = 0.93. At sites with an eccentric lumen, significant disagreement between angiography and ultrasound diameter is evident, r = 0.78. Correlation between angiography and ultrasound from percent stenosis is moderate, r = 0.63. Following balloon angioplasty percutaneous transluminal coronary angioplasty (PTCA), morphologic findings include complex cracks, splits, and dissections, and minimum lumen diameter by angiography and intravascular ultrasound correlate poorly. Recent advances have improved the utility of coronary ultrasound, including smaller catheters and a device combining a miniature imaging transducer (1.16 mm) with a low profile balloon (0.028–0.033 inch). Important current limitations include inability to visualize the smallest coronaries and tight stensoses. The future of coronary ultrasound is promising, propelled by the unique capability of this modality to image atherosclerotic plaques directly.

(Am J Cardiol 1992;69:18H–29H)

For >3 decades, angiography has constituted the "gold standard" for evaluation of atherosclerotic coronary artery disease (CAD). Although cineangiography is universally accepted, many investigators have raised important questions regarding the diagnostic accuracy of radiographic methods for coronary evaluation.[1–8] Despite these doubts, alternative methods for assessment of the severity of coronary disease did not exist and angiography evolved as the principal means used to select patients for medical or surgical therapy. With the development of transcatheter therapeutic techniques such as balloon percutaneous transluminal coronary angioplasty (PTCA), angiography quickly became the standard criterion for the selection of patients and lesions suitable for dilation. Angiography also is widely employed as the exclusive imaging modality used to guide therapeutic procedures and evaluate the adequacy of results.

In the 1980s, advances in technology have yielded the first practical alternative to angiography for diagnostic evaluation of CAD. New electronic and acoustic technology has permitted the development of miniaturized intravascular ultrasound systems capable of real-time coronary imaging.[9–19] Intraluminal ultrasound has several unique characteristics valuable in the detection and quantitation of CAD. The tomographic orientation of intravascular imaging offers a fundamentally different perspective for evaluation of the anatomic severity of coronary obstructions. Available data indicate

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that cross-sectional coronary dimensions obtained by intravascular ultrasound are frequently divergent from angiographic measurements.

Intraluminal imaging enables identification of some anatomic features invisible to radiographic methods. The unique ability of ultrasound to characterize soft tissue permits morphologic evaluation of the structure of the vessel wall. Thus, intravascular ultrasound is the first imaging method capable of directly visualizing atherosclerotic coronary lesions in vivo. Necropsy studies suggest that the composition of atherosclerotic plaques is an important determinant of their biologic behavior.[5] Accordingly, morphologic evaluation of the coronary wall has the potential of providing valuable insights into the pathophysiology, diagnosis, and treatment of CAD.

INTRAVASCULAR ULTRASOUND

Rationale: The limitations of radiographic methods for assessment of CAD provide an important element of the rationale for development of intraluminal imaging techniques. Clinical studies have documented substantial intra- and interobserver variability in the interpretation of coronary angiograms.[7,8] Necropsy studies have described significant discrepancy between the angiographic extent of disease and subsequent histologic examination.[1–6] Recently, investigations have demonstrated a dissociation between the apparent severity of stenoses by angiography and the physiologic consequences of coronary lesions assessed by measuring hyperemic flow reserve.[20]

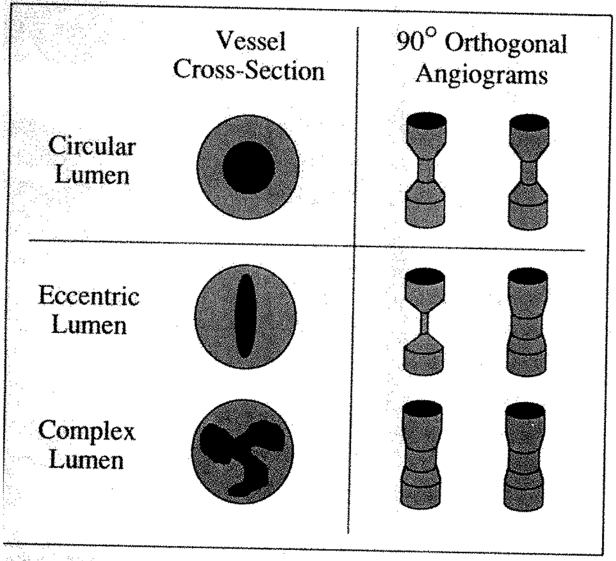

FIGURE 1. Theoretical impact of lumen eccentricity on angiographic appearance. In the *left panel*, a series of vessel cross-sections are illustrated. In the *right panel*, the angiographic appearance of these lesions is illustrated. For complex, eccentric lumen shapes, no angle of view may accurately depict the true stenosis severity.

The large variability and poor reproducibility of angiography should not be surprising. Examination of histologic cross-sections obtained from atherosclerotic coronary arteries often demonstrate a complex and eccentric lumen. Cineangiography depicts this complex vascular anatomy as a planar silhouette of a contrast-filled vessel lumen. Accordingly, any single projection may significantly misrepresent the extent of luminal narrowing (Figure 1). Theoretically, 2 orthogonal angiograms should adequately portray most lesions, but orthogonal views may be unobtainable, particularly at bifurcation sites and for segments with extreme curvature. Even when unlimited orthogonal views are available, biplane angiography remains accurate only for relatively simple luminal shapes (Figure 1b). Postmortem studies demonstrate that some coronary lesions are so complex that no combination of angiographic views will accurately depict the extent of narrowing (Figure 1c).

An additional limitation of angiography arises from the customary practice of describing lesion severity using calculations of percent luminal area reduction. Necropsy studies have emphasized that CAD is usually diffuse and contains no truly normal segment from which to calculate percent stenosis accurately.[3–6] When diffuse disease is present, measurements of angiographic percent luminal reduction will always underestimate lesion severity (Figure 2). An additional confounding variable is the phenomenon known as "coronary remodeling"—defined as compensatory dilation at the site of atherosclerotic luminal encroachment.[21]

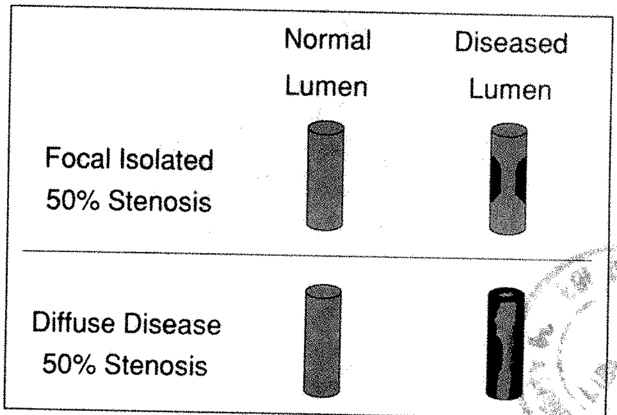

FIGURE 2. Effect of diffuse disease on percent stenosis determination. In the *top panel*, a discrete luminal narrowing superimposed on an otherwise normal vessel produces a 50% stenosis. In the *bottom panel*, a more severe luminal narrowing is superimposed on a diffusely diseased vessel, also yielding a 50% stenosis.

Thus, uncertainty remains whether a given segment is truly normal, diffusely diseased, or even ectatic. Such uncertainty undermines the reliability of percent stenosis measurements.

Advantages: Intravascular ultrasound has several unique properties that are theoretically valuable in the detection and quantitation of coronary disease. The cross-sectional perspective of intravascular ultrasound permits visualization of the full circumference of the vessel wall from a single tomographic view. Measurements of the lumen area are not dependent on the radiographic projection and can be determined by planimetry directly from the ultrasound image. The cross-sectional orientation of intraluminal imaging permits visualization of segments notoriously difficult to image by radiography, including bifurcation sites and coronaries obscured by overlapping vessels.

The ability of ultrasound to characterize wall structure permits quantitative assessment of normal and abnormal intramural anatomy. Intravascular cross-sectional imaging enables precise measurements of the thickness and echogenicity of the vessel wall layers to determine plaque area and composition. Measurements of wall morphology can detect diffuse disease concealed in angiographically "normal" segments. Theoretically, plaque measurement should provide the most precise method yet developed to quantify atherosclerosis regression or progression.

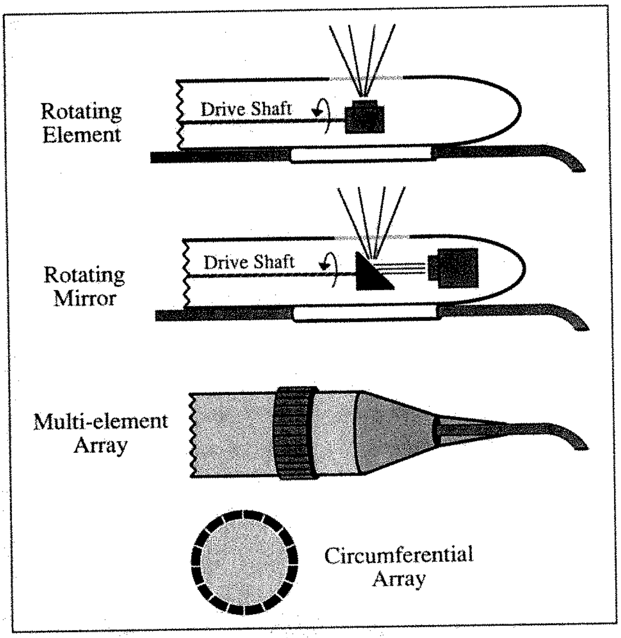

FIGURE 3. Alternative designs for intravascular ultrasound devices. In the *top panel*, the transducer is rotated directly by a drive shaft. In the *middle panel*, the transducer is fixed at the catheter tip and an acoustic mirror is rotated. This design reduces ring-down artifact (see text). In the *bottom panel*, an electronic design with no moving parts is illustrated. The mechanical design uses a monorail guide wire, whereas the electronic system employes a central lumen wire.

The theoretical advantages of ultrasound for quantitation of atherosclerosis are routinely used in the transcutaneous evaluation of peripheral vascular disease.[3] However, attempts to image the coronary by transthoracic or transesophageal echocardiography have achieved limited success, in part because the ultrasound frequencies required to penetrate the chest wall are too low to permit high-resolution imaging. Intraoperative placement of epicardial high-frequency transducers generates excellent images and has provided valuable insights into coronary atherosclerosis, but is impractical for routine clinical examinations.[22] By placing the transducer at the tip of an angiographic catheter, intravascular ultrasound offers major advantages for high resolution imaging of the coronaries. Since the transducer is placed in close proximity to the vessel wall, intravascular imaging devices can employ high frequencies (20–50 MHz) that provide excellent theoretical resolution (axial <100 μm and lateral <250 μm).

Development: Initial efforts to develop miniaturized transducers for intravascular ultrasound imaging began nearly 20 years ago, but only recently have such efforts yielded success.[9–19] Two dissimilar technical approaches to intraluminal transducer design have emerged: mechanically rotated devices and multielement electronic arrays (Figure 3). Both approaches have advantages and disadvantages. Multielement designs yield catheters with greater mechanical flexibility, whereas rotating probes generally offer greater acoustic power. Gradual progress with each type of design has resulted in small intravascular devices suitable for coronary imaging (1.1–1.8 mm in diameter). Current systems typically generate images at 10–30 frames/sec for storage on videotape.

Visualization of small coronary vessels necessitates imaging close to the surface of the catheter, which requires addressing the troublesome problem of transducer ring-down artifact. The ring-down phenomenon is characterized by high amplitude oscillations of the piezoelectric transducer material that obscure near-field structures. Early mechanical probe designs utilized a small ultrasound element directly rotated by a drive shaft that traversed the length of the catheter (Figure 3, top panel). Improved designs now employ a rotating acoustic mirror to permit a longer signal path from the transducer to the vessel lumen (Figure 3, middle panel). This modification confines the ring-down signal within the catheter and permits imaging close to the surface of the device. In electronic array devices, the transducer is surface mounted, but the ring-down can be reduced or eliminated by digital subtraction.[17,19]

For safe coronary imaging, the transducer-tipped catheter must be small and flexible to enable safe passage into the tortuous vessels frequently encountered in patients. For both mechanical and electronic designs, a moveable guide wire is usually employed to facilitate subselective coronary cannulation. Current technology has permitted reduction of mechanical probe sizes to 3.9 F (1.30 mm) and electronic designs to 3.5 F (1.17 mm). However, normal first order epicardial coronaries typically are 2.0–5.0 mm, and atherosclerotic lumina can reach 0.1 mm. Accordingly, no probe is currently capable of imaging moderately severe stenoses prior to balloon angioplasty.

Safety of human coronary ultrasound: Although intracoronary instrumentation is required, initial studies of intravascular ultrasound during diagnostic catheterization have demonstrated few serious untoward effects.[17–19] Transient coronary spasm has been noted and the transducer can occlude flow when advanced into stenoses or small distal vessels. However, patients generally do not experience chest pain if the catheter is promptly withdrawn. Most protocols avoid instrumentation of arteries with an estimated coronary diameter too small to accommodate the device safely (3.5–5.5 F, 1.17–1.83 mm). Intravascular ultrasound has also been performed with few untoward effects in large numbers of patients following PTCA, atherectomy, or other interventional procedures.[18,23] Some investigators have studied patients with acute coronary syndromes, including unstable angina and immediately following myocardial infarction.[24]

Theoretical risks such as acute coronary thrombosis or dissection have not been encountered and no deaths have been reported. Systemic administration of heparin (5,000–10,000 U) is routinely employed by most investigators prior to subselective coronary cannulation. However, there are no controlled studies of the necessity for anticoagulation and we have safely examined >50 patients using only 3,000 U of heparin administered prior to angiography. The lack of reported significant adverse effects demonstrates that coronary intravascular ultrasound is quite safe when employed as an adjunct to diagnostic or therapeutic cardiac catheterization.

MORPHOLOGY

Normal coronary anatomy: Much of our understanding of vessel anatomy by intravascular ultrasound has been derived from studies comparing ultrasound images obtained in vitro with histologic cross-sections of the same vessel.[25–27] However, there are important differences between ultrasound anatomy visualized in vitro and in vivo. Because necropsy specimens are not distended by physiologic pressure, elastic recoil can reduce the lumen to a cross-sectional area $<33\%$ of the in vivo size. In vitro, the shrinkage of vessel wall tissues results in a bunching or corrugation of intramural structures, which alters the acoustic properties of the tissue.[28]

Alterations in ultrasound appearance in vessels studied postmortem can dramatically affect image interpretation.[28] Distended by physiologic pressures in vivo, the intimal leading edge is frequently of minimal acoustic reflectance, particularly for normal segments. Postmortem, this acoustic interface is exaggerated by shrinkage artifact yielding a more echogenic appearance. In vitro the media assume a prominent sonolucent appearance and ultrasound exhibits distinct acoustic interfaces between intima, media, and adventitia. In vivo, these anatomic landmarks are more indistinct and the sonolucent band is reduced in thickness.

Some investigators, including those in our laboratory, have examined wall morphology in normal subjects studied in vivo.[19,29] Mean and standard deviation values obtained in normal subjects were used to classify abnormalities in patients with atherosclerotic CAD.[19] A distinctly laminar appearance to the normal vessel wall is reported in many, but not all normal persons, although the genesis of these ultrasound layers remains controversial. In some normal subjects, a discrete linear ultrasonic reflectance is observed at the acoustic interface between the lumen and intima (Figure 4A). However, other normal subjects sometimes exhibit an intimal leading edge that poorly reflects ultrasound, a phenomenon that leads to *dropout* of ultrasound signals (Figure 4B) Thus, distinct laminations of the vessel wall are absent at 30–50% of the coronary sites in normal persons.[19,29]

When an intimal leading edge is observed, the maximal thickness averages <0.20 mm and most investigators consider a normal value to be <0.20–0.30 mm.[18,19,29] These values are larger than the histologic thickness of the intima and reflect the intrinsic axial resolution of the ultrasound device, not precise anatomic boundaries. A distinct subintimal sonolucent layer is often evident in normal segments (50–70% of normal subjects), with a maximal thickness averaging <0.20 mm. One hypothesis proposes that the characteristic sonolucent zone represents normal media; however, differences in the ultrasound anatomy of muscular (usually laminar) and elastic arteries (usually monolayered) have been reported. Some of the disparate findings in normal subjects may also reflect dissimilarities in instrumentation (electronic vs mechanical probes) or selection of normal subjects (young vs old).

Coronary atherosclerosis: A variety of intravascular ultrasound features are prevalent in patients with atherosclerotic CAD. The thickness of the intimal leading edge or sonolucent zone is abnormally increased in many coronary disease patients, although the ultrasound appearance differs significantly among available imaging devices. Mechanical ultrasound probes typically visualize coronary plaques as intramural structures with variable echogenicity and intraluminal encroachment, usually with a thin sonolucent subintimal band reported by some investigators to represent normal media.[25-27] This classification may represent an oversimplification—necropsy studies demonstrate that the media are often attenuated or completely absent in some atherosclerotic segments. The thickness of the "medial lucency" may also be affected by acoustic shadowing and other confounding variables.

Other investigators using electronic probes report a radically different appearance of athereosclerotic plaques.[17,19] In diseased segments, the multielement devices often visualize a variably increased intimal leading edge, sometimes with a distinctly thickened sonolucent subintimal band thought to represent atherosclerotic plaque of low acoustic reflectance (Figure 5). These differences in instrumentation have slowed universal acceptance of a single classification scheme for coronary ultrasound images. Regardless of transducer design, it must also be emphasized that ultrasound provides images based on the acoustic reflectance of tissue, not actual histologic results. Thus, tissue composition is inferred from the echogenicity and texture of structures imaged by ultrasound, an inherently imprecise approach.

With either mechanical or electronic devices, atherosclerotic vessels often exhibit both abnormal thickening and increased echogenicity of the intimal leading edge (Figure 6). Commonly described as "hard plaques," these echogenic structures presumably represent layers with intimal fibrosis that produce specular ultrasound reflections. In the most extreme examples, heavily fibrotic or calcified intimal layer lesions reduce transmission of the low energy, high frequency ultrasound signals, thus obscuring the underlying structure of the arterial wall. When extensive, "shadowing" plaques can preclude measurement of total atheroma area because the full thickness of the vessel wall is concealed.

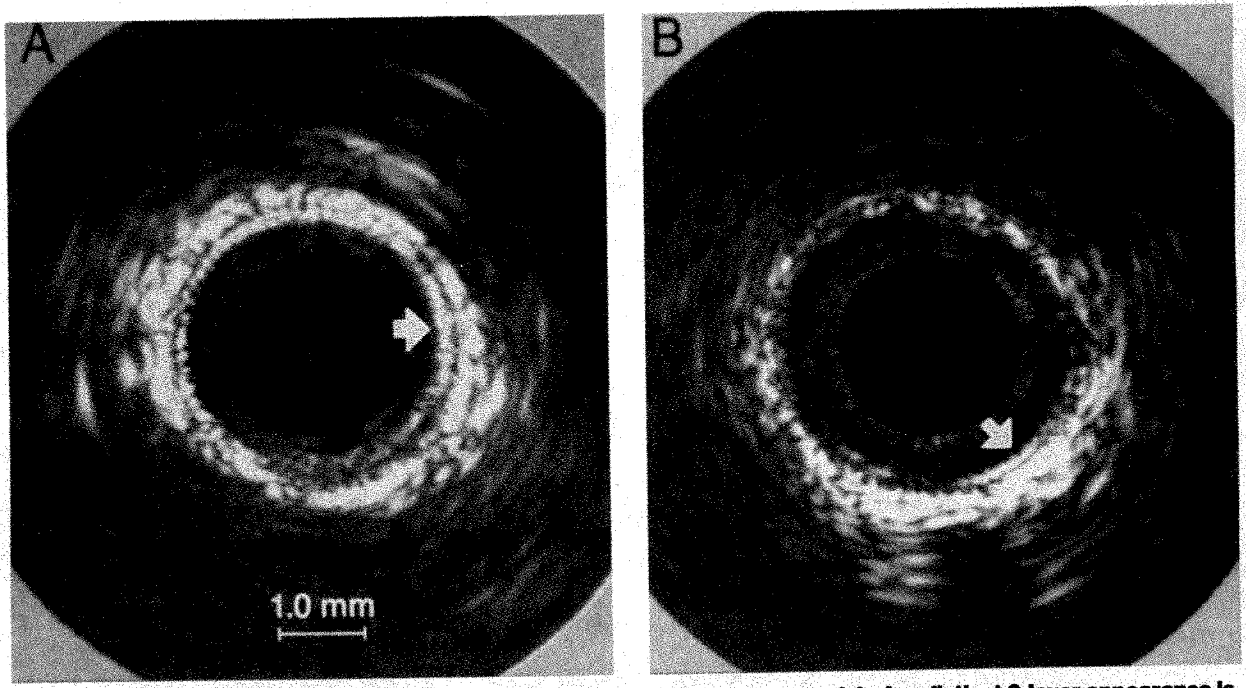

FIGURE 4. Two variants of normal coronary anatomy by intravascular ultrasound. In *A*, a distinct 3-layer appearance is evident with a thin intimal leading edge and sonolucent zone (arrow). In *B*, there is dropout of the intimal leading edge except for the zone indicated by the arrow.

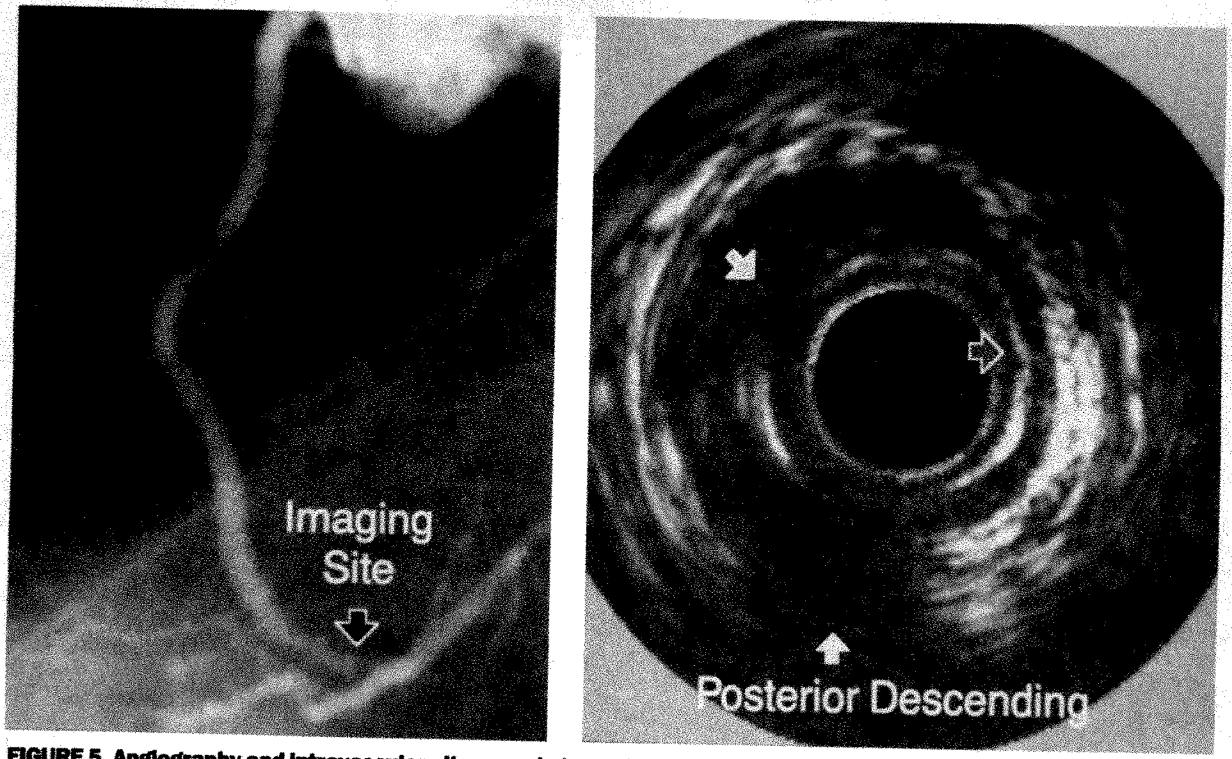

FIGURE 5. Angiography and intravascular ultrasound at an atherosclerotic site in the right coronary artery. In the *left panel*, the imaging site is indicated by the black arrow. In the *right panel*, the sonolucent zone is greatly expanded (light gray arrow), while the intimal leading edge remains normal in the thickness (dark gray arrow). The vessel wall overlying the sonolucent plaque is expanded outward, indicating remodeling.

Intravascular ultrasound in segments containing an angiographic luminal irregularity frequently reveals a crescentic sonolucent band encroaching on the lumen (Figure 5). In many patients, both lesions, thickening of the intimal leading edge and broad sonolucent plaques, coexist at a single site or at different locations (Figure 6). At some sites, the sonolucent band is thickened but symmetrical, lending a distinctive triple-layered appearance to the ultrasound image (Figure 7). In most arteries, the adventitia appears as a third, deeper layer of the vessel wall and varies considerably in appearance (Figures 4–7). A distinct interface at the trailing edge of this adventitial layer is not apparent except within bypass grafts. Since this layer likely represents the tissues encasing the vessel, the ambiguity of the trailing edge often precludes measurement of total vessel wall thickness.

Angiographically normal sites: In most patients with CAD, intravascular ultrasound demonstrates atherosclerotic abnormalities in coronary wall morphology at sites with no lesion present on angiography.[19,29–30] In the presence of any angiographic luminal irregularity, intravascular ultrasound frequently demonstrates CAD at all other examined coronary sites. In one study, intravascular ultrasound abnormalities were detected at >75% of angiographically normal sites in CAD patients.[30] The extent of atherosclerosis in angiographically normal vessels confirms the finding, previously reported from necropsy studies, that coronary disease is frequently more diffuse than apparent by angiography. In some cases, it is

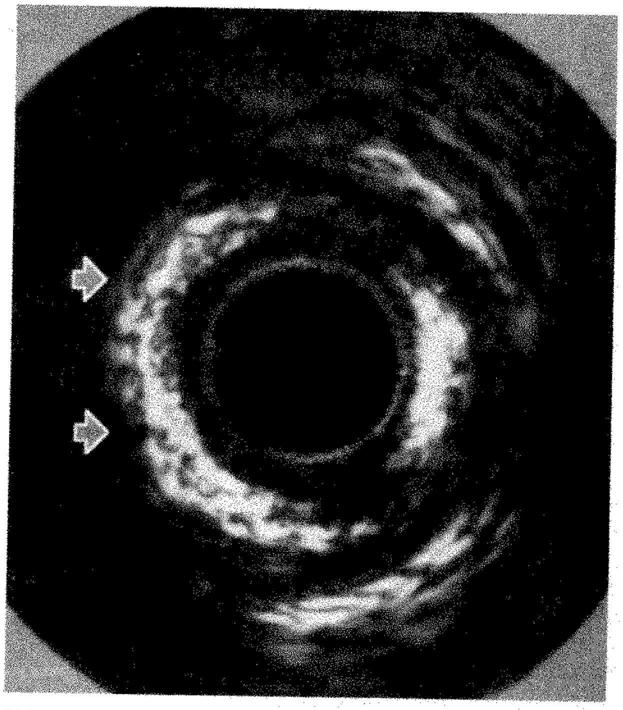

FIGURE 6. Ultrasound image showing dense "hard" plaque. The arrows identify a greatly thickened intimal leading edge that obstructs ultrasound transmission, thus shadowing underlying structures.

evident that preservation of angiographic lumen size is a consequence of compensatory remodeling of the vessel wall (Figure 5).

QUANTITATIVE LUMINAL MEASUREMENTS

Because atherosclerotic coronary arteries in patients are frequently complex and eccentric, we anticipated that a tomographic imaging technique such as intravascular ultrasound might yield measurements that differed significantly from angiography. Accordingly, we compared luminal dimensions by angiography and ultrasound in a series of patients undergoing diagnostic or therapeutic catheterization.[19] For each coronary site examined, the cineangiogram was magnified and the vessel dimension measured for the angiographic projection demonstrating minimum coronary diameter. Magnification correction was performed using the measured size and known diameter of the guiding catheter. At stenosis sites, angiographic cross-sectional area reduction was calculated from diameter measurements.

Analysis of ultrasound images was performed using an electronic cursor to measure images digitized from videotape. For each measured site, 10-second intravascular ultrasound segments were digitized to enable review of full motion imaging sequences. This process assisted the identification of luminal borders and helped confirm the precise location of vascular wall structures. In addition, injection of iodinated contrast medium during imaging was used to produce luminal opacification. Comparison of images with and without contrast

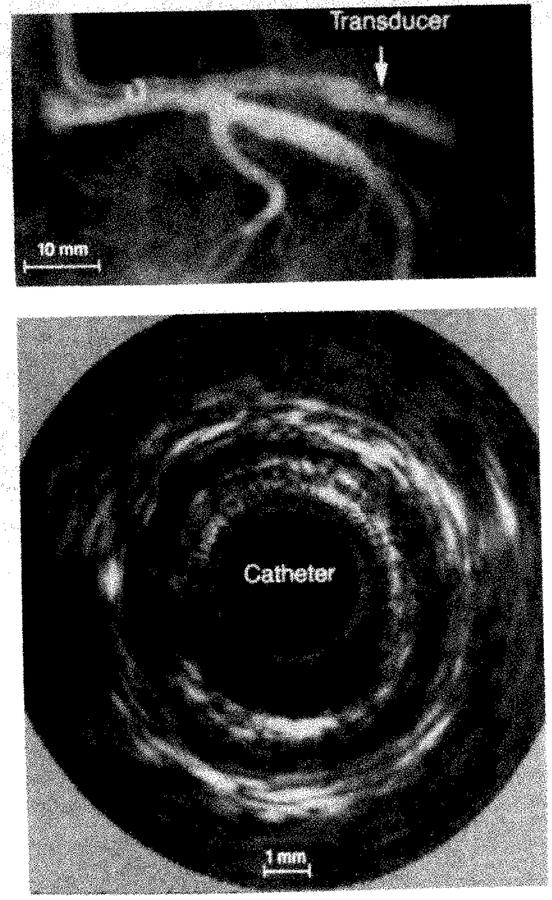

FIGURE 7. Angiographic site and intravascular ultrasound showing diffuse concentric atherosclerosis. Both the intimal leading edge and sonolucent zone are thickened, resulting in an exaggerated trilaminar appearance to the artery.

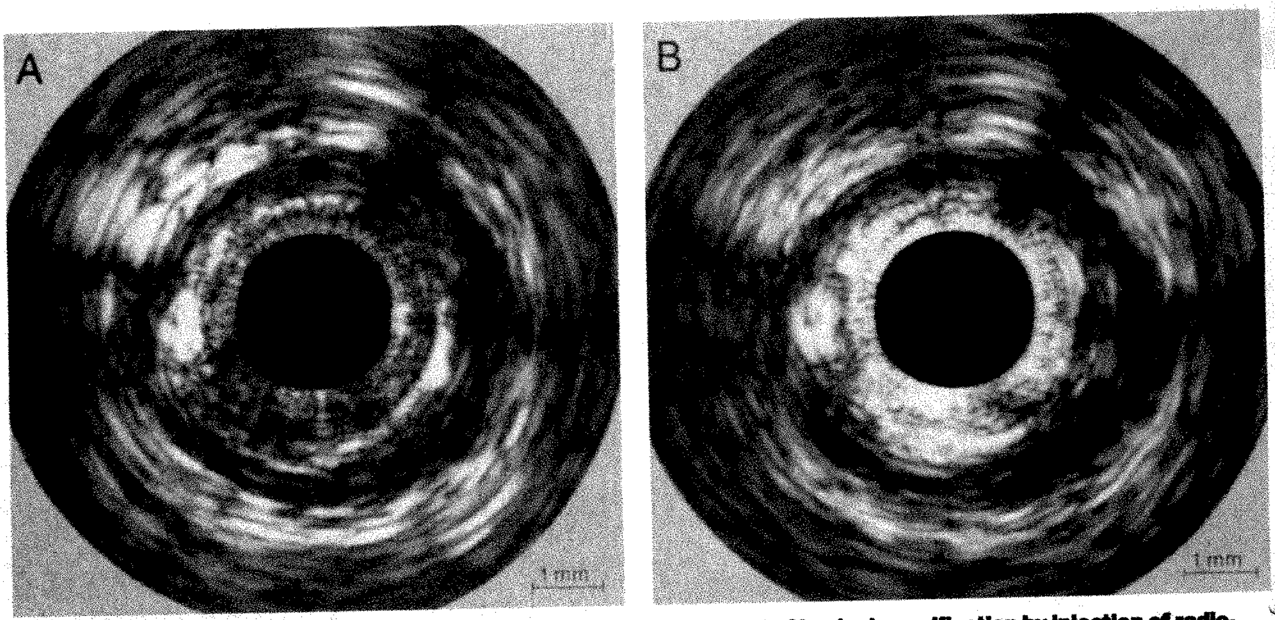

FIGURE 8. Intravascular ultrasound before (*A*) and after (*B*) enhancement of luminal opacification by injection of radiographic contrast.

enhancement aided in the identification of the intimal leading edge (Figure 8).

We sought to determine the impact of vessel eccentricity on the comparison of dimensions by angiography and ultrasound. A standardized computer index of eccentricity, the circular shape factor, was calculated to determine the degree of deviation of the lumen from a circular cross-section. For each site, the cross-sectional area was planimetered with an electronic cursor. This measured lumen area was used to calculate a mean vessel diameter as:

$$d = 2\sqrt{\frac{\mathrm{CSA}}{\pi}}$$

(where CSA is the cross-sectional area). The smallest possible perimeter for a lumen with this diameter (a perfect circle) was calculated as $P = \pi d$ (where P is the perimeter). The calculated perimeter was compared to the actual perimeter of the vessel lumen as measured by planimetry. The calculation yields a computer index of eccentricity, the circular shape factor, defined as:

$$\mathrm{CSF} = \left(\frac{\text{calculated perimeter}}{\text{observed perimeter}}\right)^2$$

where CSF is the circular shape factor (Figure 9). An index of 1.0 is a perfect circle and smaller values indicate progressively greater eccentricity.

We performed analyses for three subgroups: normal subjects and two separate categories of CAD sites, segments with a concentric versus an eccentric lumen shape. In the normal subjects, the circular shape factor averaged 0.92 ± 0.2, illustrating the nearly circular lumen shape evident in patients with normal coronary arteries. In these normal subjects, the correlation between angiographic and ultrasound coronary diameter for normal subjects was close, r = 0.92. Thus, intravascular ultrasound and angiography yield comparable measurements of lumen size in normal, nonatherosclerotic arteries with a circular lumen profile.

In approximately 67% of CAD segments, the diseased lumen remained concentric in shape (CSF >0.92) and the correlation between ultrasound and angiography was also close, r = 93. However, the subgroup of CAD patients with an eccentric lumen demonstrated significant disagreement between angiography and ultrasound diameter, r = 0.78. We believe this reduced correlation is explained by the irregular, noncircular lumen shape encountered in these atherosclerotic vessels. These data demonstrate the potential superiority of a tomographic technique, such as intravascular ultrasound, in measurement of minimum coronary diameter for the complex eccentric lumen shapes encountered in some patients with CAD.

Focal stenoses were identified by both angiography and ultrasound at 41 sites. Cross-sectional area reduction was calculated from angiography using diameter measurements. At identical sites, steno-

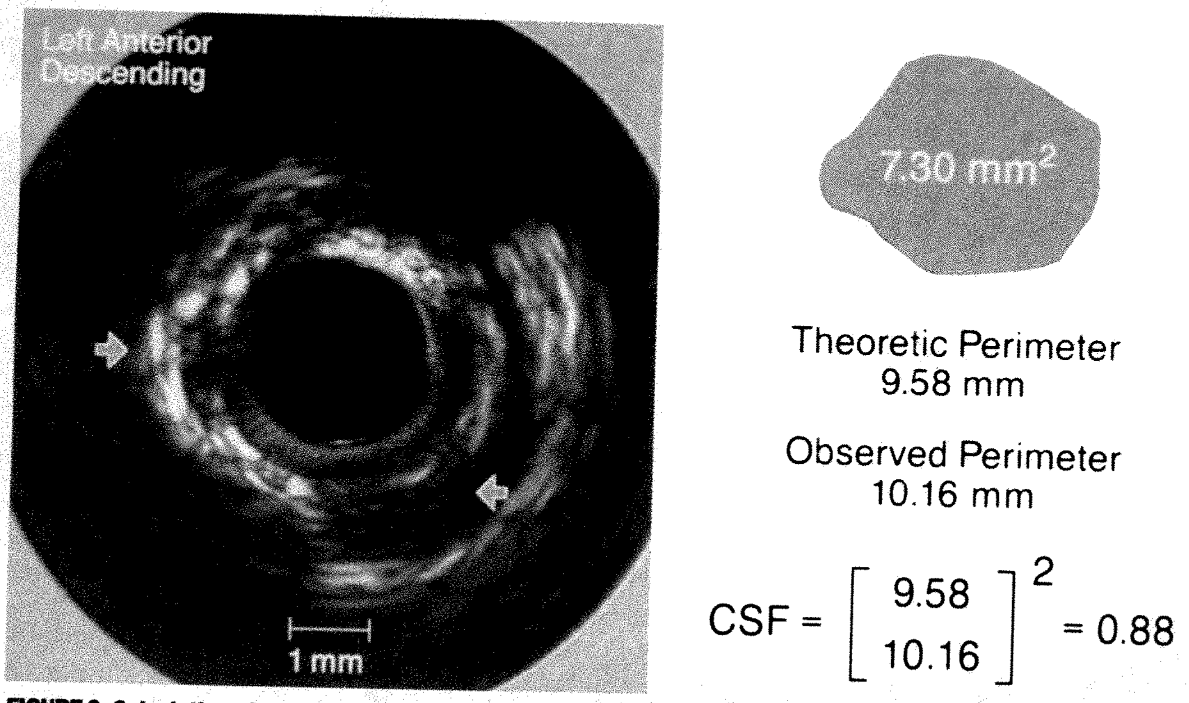

FIGURE 9. Calculation of the circular shape factor (CSF). The CSF value of 0.88 indicates moderate eccentricity.

sis measurements from digitized ultrasound images were performed by planimetry of the lumen. Mean stenosis severity, expressed as percent luminal area reduction, was similar by cineangiography, 48.9 ± 13.8%, and intravascular ultrasound, 52.3 ± 16.3% ($p = 0.10$).[8,27] However, the correlation between percent stenosis by cineangiography and ultrasound was only moderate, $r = 0.63$. These data demonstrate that there are important differences between ultrasonic and angiographic assessment of stenosis severity.

EVALUATION OF ANGIOPLASTY RESULTS

Comparison of luminal dimensions by angiography and ultrasound for vessels examined immediately following angioplasty demonstrates a poor correlation between minimum luminal diameter by angiography and intravascular ultrasound.[18,31] These results should not be surprising, because it is recognized that balloon dilation distorts the vessel wall, generating complex and eccentric luminal shapes.[32] Measurements of luminal cross-sectional area following angioplasty are generally smaller by ultrasound than angiography. Following PTCA, a diverse spectrum of ultrasound morphologic findings are common, including complex cracks, splits, and dissections in the vessel wall.[18,19,31] The larger lumen sizes evident by angiography may represent enhancement of the apparent angiographic diameter of the vessel produced by extraluminal contrast within these cracks or splits in the intima and/or media of the vessel. The angiographic image in such cases is often described as having a "hazy" lumen and may represent primary failure of PTCA.

Intravascular ultrasound has other potentially important applications in guiding angioplasty and evaluating PTCA results. Identification of a truly normal reference segment for balloon sizing represents a significant clinical problem in angioplasty. Intravascular ultrasound permits independent evaluation of the dimensions and extent of intramural disease in "normal" segments and may prove to be a useful adjunct for balloon sizing.

Some investigators have speculated that intravascular ultrasound would be particularly valuable in detecting angioplasty-related complications such as dissection or intraluminal thrombus.[18] However, it can be quite difficult to distinguish therapeutic from pathologic dissection by intravascular ultrasound. The acoustic properties of thrombus are similar to blood and may be difficult to differentiate. Improvements in image quality, including greater acoustic power and higher frequencies, may enable more accurate identification of intraluminal thrombus. Injection of microbubble contrast media is often helpful in identifying dissections and may aid in the identification of thrombus.

Recent technologic developments have improved the utility of ultrasound as a means of guiding and evaluating PTCA. These advances include smaller and more flexible catheters with sizes approaching 1.0 mm. One important catheter development combines an intravascular ultrasound array and a low-profile PTCA balloon in a single device.[33] The device incorporates a multi-element imaging array positioned a few millimeters proximal to the dilating balloon. The combination angioplasty and imaging system allows the operator to perform a balloon inflation, then slightly advance the catheter to examine the PTCA site. This procedure enables evaluation of lumen size and wall morphology after each inflation without the necessity for catheter exchanges (Figure 10).

Current research is attempting to define the relationship between ultrasound appearance and PTCA results. Intravascular imaging appears particularly promising as a means to evaluate phenomena such as abrupt occlusion and restenosis. Long-term studies comparing ultrasound appearance and clinical outcome will be required to establish the ultimate value of intravascular ultrasound following angioplasty. Such multicenter studies will require greater standardization in instrumentation and consensus on the optimal criteria for image interpretation.

LIMITATIONS OF INTRAVASCULAR ULTRASOUND

Despite considerable technical progress, there remain important limitations to intravascular ultrasound imaging of the coronaries. The physical size of current devices does not permit imaging of small coronaries or tight stenoses and precludes examination of most lesions prior to balloon angioplasty. The smallest size of currently available coronary imaging devices is slightly >1.0 mm. This size barrier may be difficult to surpass because of the physics of high frequency ultrasound and the properties of currently available transducer materials. Further reductions in transducer size may also be limited because transducer miniaturization reduces available acoustic power and thus compromises signal-to-noise ratio. The phenomenon of transducer ring-down also complicates development of devices capable of imaging small vessels. Because of ring-down artifacts, all current devices have a larger "acoustic size" than physical size.

Current intravascular ultrasound devices employ very low acoustic power to produce images. Normal subjects often have an intimal leading edge of minimal acoustic reflectance and this delicate interface may poorly reflect ultrasound, a phenomenon that leads to "dropout" of ultrasound signals. Although dropout is frequently observed in normal segments, it is less prevalent in diseased vessels.[19] The opposite problem, "shadowing" by calcific plaque, can obscure the underlying structure of the arterial wall. The heavily fibrotic or calcified intimal atherosclerosis impedes transmission of the low energy, high frequency ultrasound signals utilized for intravascular imaging. Presence of shadowing plaques may preclude measurement of atheroma area because the full thickness of the vessel wall is obscured.

Several properties of intraluminal devices are capable of generating artifacts that may affect quantitative measurements. For systems with mechanical transducers, rotation speed may increase or decrease because of mechanical drag, particularly when the drive shaft is bent by a tortuous coronary. The resulting nonuniform rotational velocity produces a distinctive and troublesome distortion of the image. Improvements in the mechanical precision of these devices have reduced, but not eliminated, nonuniform rotational distortion.

All tomographic imaging techniques, including intravascular ultrasound, are vulnerable to distortion produced by oblique imaging planes. Thus, a vessel with a circular cross-sectional profile will appear elliptical whenever the transducer is not orthogonal to the long axis of the vessel. This phenomenon can represent a confounding variable in quantitative measurements. However, nonorthogonal orientation is more prevalent in the larger vessels encountered during peripheral vascular imaging, for the small size of the coronaries limits the extent of angulation.

FUTURE RESEARCH AND DEVELOPMENT

The technology and clinical role for intravascular ultrasound examination of the coronary arteries are still rapidly evolving. Important technical advances include further reductions in the size of imaging catheters and development of improved devices combining diagnostic and therapeutic capability. Catheters combining a small imaging transducer (1.16 mm) and low-profile angioplasty balloon (0.028–0.033 inch) are undergoing large-scale trials. Other investigational approaches include transducers mounted on atherectomy devices and laser delivery systems. If such devices provide practical assistance to revascularization procedures, combination imaging and therapy devices have the potential of becoming the future standard for angioplasty techniques.[33,34]

Imaging catheters that incorporate a tip-mounted Doppler flow probe to allow simultaneous cross-sectional area and flow velocity measurements are also under development. Such devices may provide continuous beat-to-beat assessment of coronary blood flow in vivo. Other proposed developments included "forward looking"

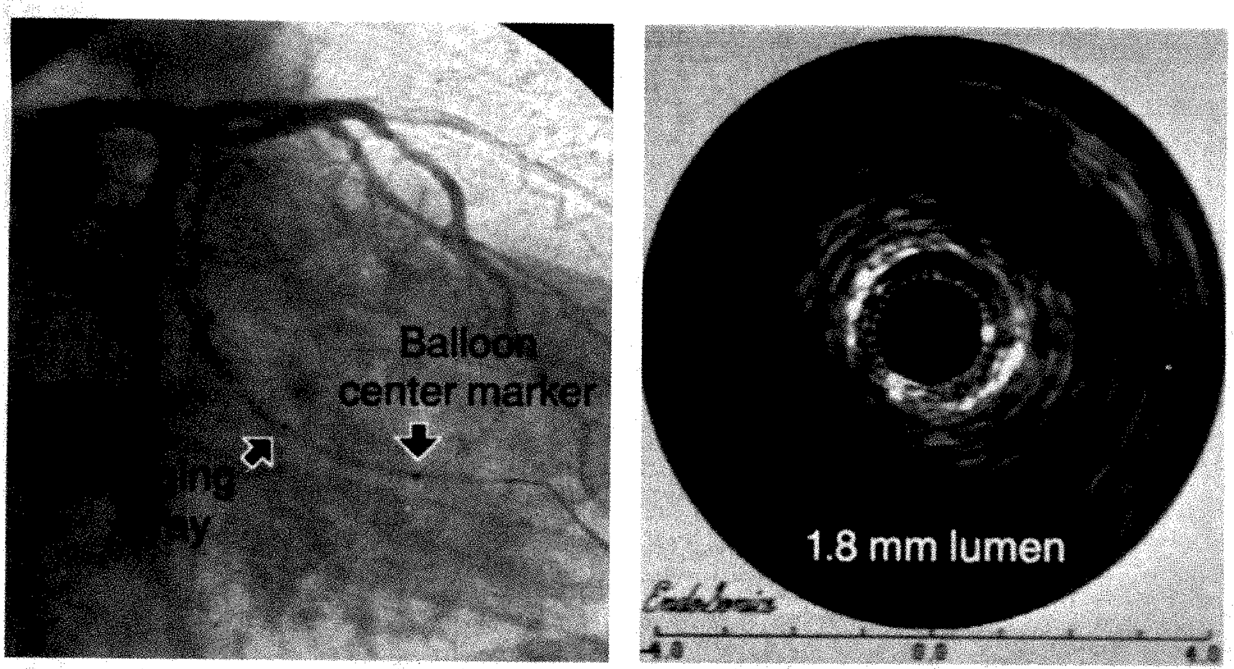

FIGURE 10. Application of a device combining an imaging array with an angioplasty balloon. The transducer is located proximal to the balloon, permitting a low-profile device.

probes with the ability to examine downstream sites to permit imaging of coronaries with diameters smaller than existing transducers. Other research is examining the utility of 3-dimensional reconstruction of a series of tomographic coronary images.[35] Although visually appealing, 3-dimensional reconstructions are largely artificial because the images are generated during a pull-back through a coronary segment. During the pull-back procedure, the transducer invariably shifts position or angulation in the lumen, a confounding variable not accounted for by current reconstruction techniques.

EMERGING APPLICATIONS FOR CORONARY ULTRASOUND

Published studies support several emerging applications for intravascular ultrasound. Precision measurements of coronary luminal diameter and cross-sectional area may have incremental value in assessment of eccentrically diseased vessels. The tomographic perspective of intravascular ultrasound is likely superior to planar methods such as angiography for cross-sectional area measurement. The advantages of tomographic imaging are particularly evident in the assessment of the results of these catheter-based revascularization procedures because it is difficult for angiography to characterize the complex alterations in the vessel wall produced by balloon, laser or atherectomy procedures.

Unlike angiography, which depicts only the effects of atherosclerosis on the lumen, intravascular ultrasound permits evaluation of the actual pathologic site of the disease. The ability to image atherosclerotic wall abnormalities in vivo has considerable research potential. Coronary ultrasound is currently contributing to scientific understanding of the anatomy and pathophysiology of CAD, including the plaque features associated with conversion from stable to unstable angina.[24] Measurements of the size and morphologic characteristics of plaques will enable more precise quantitation of disease progression, including the effects of pharmacologic or dietary interventions.

Intravascular ultrasound has demonstrated greater sensitivity than angiography in the detection of CAD and commonly detects atherosclerosis in angiographically normal segments. Striking atherosclerotic abnormalities are occasionally evident in patients with totally normal coronaries by angiography. Based on this finding, it can be argued that a patient should not be dismissed as possessing normal coronaries based exclusively on angiographic images. Intravascular ultrasound has also been applied to evaluation of angiographically normal coronary arteries following cardiac transplantation, often revealing occult intimal thickening.

The indications for intravascular ultrasound during coronary angioplasty continue to evolve. Ultrasound imaging provides precise measurements of the cross-sectional area of the residual lumen and atheroma. The morphology of the vessel wall following revascularization may hold important clues to phenomena such as restenosis and abrupt occlusion. However, the ultimate value of ultrasound anatomy in predicting the short- and long-term complications of angioplasty is not yet defined. The development of combined imaging and therapy devices will likely expand the utility of ultrasound imaging following PTCA. The unique tomographic perspective of coronary intravascular ultrasound and the ability to image atherosclerotic plaques directly ensure a prominent role for this technology in the cardiac catheterization laboratory of the future.

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Discussion I: Intravascular Ultrasound

Dr. Anthony DeMaria (Lexington, Kentucky): Our first panel will discuss important aspects of intravascular ultrasound. Joining the speakers are Drs. Andrew Weintraub, Paul Grayburn, and Martin Goldman. I will begin by asking Dr. Kerber, a pioneer in the field: Do you see epicardial imaging interacting with intravascular ultrasound other than in the operating room?

Dr. Richard Kerber (Iowa City, Iowa): Epicardial imaging will remain primarily an operating room application. We are currently doing experimental work in rabbits and other small animals in which the biosound 12 MHz epicardial transducer is used to produce femoral, and even abdominal, aortic images in rabbits with diet-induced atherosclerosis. However, in terms of clinical applications, I am not quite sure of the potential of epicardial imaging.

It is obvious from the presentations that we are going to have to learn the characteristics of each of the intravascular probing instruments, i.e., the array versus the mechanical. It seems that as the instrumentation becomes more and more specialized, with higher and higher frequencies, their capabilities must become known.

Dr. DeMaria: I think Dr. Kerber makes a good point. In fact, I was surprised to hear both Drs. Nissen and Pandian speak so enthusiastically for one approach or the other, when it seems to me questions still remain as to the difference between them.

Dr. Steven Nissen (Lexington, Kentucky): Perhaps I can shed light on this aspect, which I think emphasizes the importance of first studying normal subjects in determining the capabilities of either instrument. It is difficult to find opportunities to do so, but I believe it is fundamental. At least with the instrument that we are using, I feel fairly comfortable that I know what normal anatomy is. I can now say that if something is outside 2 standard deviations from normal, it is the conventional laboratory definition of abnormal. I think there are merits and liabilities to both the mechanical and array approaches.

Briefly, the merit of the mechanical approach is the higher amount of acoustic power. There is no way to get the same quality intracardiac images, at least from the current devices, from the array. There just is not enough acoustic power to do it. In my opinion, if you want to insert a probe in the left ventricle or the right atrium, you probably need a mechanical probe because you don't have to worry about the tortuosity of the vessels and you can get enough perspective to see structures that are a distance away from the probe. However, I think that to go into a 1.5 mm coronary artery in the posterolateral left ventricular branch will require an array probe. In short, if an intracardiac procedure is performed, I think it will be based on array technology.

Dr. Natesa Pandian (Boston, Massachusetts): My main concern is image quality. It may be too premature to decide which technology is better. Probably the best image quality I have had was with a Baum 40 MHz probe. It is so good you cannot even see the lumen, but the blood and the blood scatter are visible. In looking at real-time images with a synthetic array, I have difficulty differentiating the lumen from the wall, let alone the constituents of the wall. However, I believe technology will improve. Again, I have no personal preference regarding the instruments as long as there is a good-quality image and I can make the correct determinations from it.

Dr. Harvey Feigenbaum (Indianapolis, Indiana): At our hospital we have a small program in intravascular ultrasound and one of the greatest difficulties we have is funding. How do you finance this research? We never had this problem for most transthoracic ultrasound instrumentation. Other instruments can be costly, but these catheters are invariably expensive. The hospital cannot assume the charge. Does anyone have National Institutes of Health type of funding or other major grants to pay for this technology? I would really be interested because lack of funding has really limited our program.

Dr. Martin Goldman (New York, New York): I have been using intravascular ultrasound for several months, and recently I went back into the catheterization laboratory to get more involved. In order for this technology to really work, it will depend on the people who use the catheters and believe that it is valuable technology to be used on a daily basis, for example, to know whether a coronary artery needs to be dilated. If it cannot be used on a routine basis to obtain high-quality images cost effectively, it will serve only as an expensive research tool.

Part of the problem has been the delivery system. Dr. Nissen showed good results with the guide wire system, but some of the difficulty is in combining good image quality with the guide wire to get to the coronary artery that you want to see. Several systems are being worked on regarding this aspect now, but it is still a limitation. The challenge rests in getting to the coronary artery, in the exact location that you want, and being able to define what you're seeing in the vessel.

Angulation is also a big problem. Clearly, as Dr. DeMaria pointed out, forward imaging is essential because we must have the right information before we do angioplasty through a laser.

Perhaps future technology will provide a dual system, a laser or high-frequency ultrasound debridement and an ultrasound guidance system to sound out how far to go using the ultrasound as a guide. We must have information about the smaller vessels and lumina that we're going into, or we will have a problem.

My last comment concerns the importance of tissue characterization in defining the lesion that is going to erupt, because that is the lesion to which we should apply angioplasty. Patients who have 95% blockages do not have as much trouble as those with 60% blocks that erupt and form tight plaques. These are the lesions that we are interested in defining because an acute event could cause them to explode. Chronic lesions actually help to promote collateral circulation. Defining the dangerous plaque and identifying the potentially erupting volcano are the important diagnostic factors from a cost-effective point of view. This is especially true when considering equipment costs. The machines cost approximately $90,000–150,000 and the catheters cost approximately $500–750.

Dr. DeMaria: Dr. Grayburn, you may be one of the few panelists here who actually does both intervention and echocardiography. Where do you see operator-type priorities in the future?

Dr. Paul Grayburn (Dallas, Texas): I think there is a trade-off between image quality and steerablility of the catheter. Basically, we use the mechanical probe and I think there is no doubt that it provides better images than the phased array probe. The drawback of the mechanical probe is that it is more difficult to steer down a coronary because it is so stiff.

Another important consideration is that you really cannot cross a tight lesion with these catheters because you will provoke ST-segment elevation and ischemia. For this reason, a forward-looking device is going to be important. I think it should be theoretically possible at least to make the mechanical probe into a guide wire that could be placed inside any better angioplasty device. Some of the more conventional devices could be used by making the mechanical device into a guide wire that spins.

Dr. DeMaria: Dr. Grayburn, do you perform your own ultrasonic imaging when you do the interventions? Also, do you assist other interventionalists in interpreting the imaging performed at your hospital?

Dr. Grayburn: Yes, I'm present for all the intravascular ultrasound imaging, and I do assist other interventionalists in interpreting the images. Dr. Kerber asked earlier about defining the large sonolucent area. Possibly it is expanded media due to the atherosclerotic deposition of lipids, or a side branch coming off at an angle. It can also be a dissection. We need to be able to make these distinctions.

One possible approach is to put a proximal port on the catheter and do a contrast injection. Contrast should go behind a dissected flap, but not through lipid-infiltrated media. Obviously, tissue characterization is another possibility. Simultaneous Doppler imaging, whether with pulsed or color flow, may be useful in making these distinctions. These are directions that we need to be taking.

Also, perhaps transplant programs would help to provide simultaneous in vivo histologic results to compare with the images. The histology would help us define the images and remove some of the guesswork.

Dr. Pandian: I view this technology in an optimistic light. Although the concept is old, most of the work has been done in the last 3–4 years. The technology is still evolving and it is unfair to demand that the instrumentation show immediate results.

In terms of size, at least 2–3 companies are thinking of making an imaging wire with a small cap so it will be atraumatic. With this device, getting to a distal vessel may not be a major problem.

There is no question that in terms of understanding histology, more work needs to be done. In fact, it may be premature to categorize the atheroma morphology as the technique stands now. I believe there will be 2 families of catheters: one for therapeutic purposes, for example, the balloon valvuloplasty or atherectomy catheters, and one for research purposes. I do not have an answer to the problem of how to handle the cost for research.

Dr. Bijoy Khandheria (Rochester, Minnesota): I think the comments that Dr. Goldman made are valid in a general practice environment, but I do not think we should forget that improvements will only come with time. Changes need to be made, but the quality of instruments and catheters cannot be compromised in order to contain costs. Perhaps one way to focus research dollars is to have a few centers of excellence that are capable of producing specific research that would be clinically applicable.

I have a question, does anyone believe there will be a "turf battle" between intravascular and intracardiac imaging?

Dr. Andrew Weintraub (Boston, Massachusetts): Like Dr. Grayburn, I also perform the interventional aspects of cardiology, and a problem does exist. As Dr. Pandian pointed out, image acquisition is very important in image interpretation. We proved this in vitro, and it is a real concern that in the catheterization laboratory it is possible to alter the image so easily and interpret it so variably. I believe the technology, at least as we use it, is still an interface between the interventional laboratory and the echocardiographers. Tissue characterization will probably help to make accurate distinctions, but I think that trying to identify or differentiate soft plaque and thrombus will prove very difficult, even in vitro.

Dr. DeMaria: Even though we cannot necessarily relate the ultrasonic characteristics to the tissue characteristics, one can still classify plaques based on these ultrasonic characteristics and continue to observe them.

Dr. Michael Crawford (Albuquerque, New Mexico): One of the problems I've noticed is that when you do in vitro studies in formalin and fix the arteries, the images appear completely different on the ultrasound than the live images. Are there any thoughts on how to eliminate this problem?

Dr. DeMaria: We do have data.

Dr. Nissen: You are absolutely right. In fact, if you remove an artery from the body, it isn't necessary to formalin-fix it. Just take it from the body, let it collapse in a Petri dish and image it. The large sonolucency is the media, but the media does not appear this way in vivo. In my opinion most of what has been published regarding the correlation between ultrasound and histology is not accurate because the arteries were not pressure-fixed. However, in England, studies are now beginning with pressure-fixed hearts.

Dr. Feigenbaum is also right about the costs of technology. We are perhaps a few months away from the first image produced by a device that consists of an ultralow-profile balloon. It's as effective as any balloon used today in the catheterization laboratory, with a 2.8 F imaging array proximal to the balloon. Presently, we cannot fix the lesion before dilation. You *will* be able to fix the lesion in the future with this balloon, which operates similarly to balloons used today. Just put it across the lesion, dilate, advance, and look. Then decide if you want to dilate again. The cost is comparable to today's low-profile balloon. Because this is a disposable item and has an imaging array, it has a great advantage.

Dr. Christopher Appleton (Tucson, Arizona): There has to be a difference in cost. It is not possible to charge the same price for a balloon with an array as for one without an array.

Dr. Nissen: I have been told that the prices will be similar. Apparently, the price of the array can be readily absorbed into the overall cost of the catheter.

Dr. DeMaria: For this technology to become reimbursable, it will have to be coupled with an interventional procedure. At the moment, and in the foreseeable future, no one will provide reimbursement simply for a diagnosis. However, I believe the idea is feasible because there is the possibility of inducing spasm when traversing the lesion, and it could be avoided with such a device. Therefore, it is a necessary advancement. I think that a prototype with an imaging device in the middle of the balloon already exists.

Dr. David Skorton (Iowa City, Iowa): I have a different perspective on 2 of these issues. First, I feel that reimbursement and utility are divided into 2 separate issues. However, I think there are certain uses for intravascular ultrasound that, even at present, would be at least partially reimbursable. As Drs. Pandian and Kerber mentioned earlier, if imaging were combined with Doppler, for example, to decide when to do angioplasty and when to do bypass surgery based on coronary flow reserve, I think you probably could obtain reimbursement. One argument for reimbursement may be to save money by *not* doing an intervention.

Second, although the images vary with the different techniques, being able to establish whether or not there is diffuse disease might affect your surgical decision. In other words, the way we "package" the technique may make reimbursement possible.

Third, it will be some time before we are able to make a distinction between soft plaque and thrombus just from backscatter, which is a nonspecific measurement that basically divides tissue into 2 general categories, normal and abnormal. I would also like to know how ultrasound technology can compete with other technologies that are producing targeted agents that will label biologically relevant components of tissue. Having a contrast agent that will label a thrombotic phenomenon or an atherosclerotic phenomenon is the way to differentiate between soft plaque and thrombus. Injecting an agent where a liposome attaches to lipoprotein will show the atherosclerotic region or will attach to a fibrinogen molecule.

One further comment is that not being able to see the intima is unrelated to spatial resolution. In Doppler ultrasound, where we scatter ensembles of particles that are 8 μm in diameter, it is not the size of the interface that's significant, but rather the difference in acoustic properties. Therefore, the reason we are not seeing the intima in normal subjects is that there is tremendous variability in the acoustic properties of normal tissue. Specialists in ultrasound tissue characterization say that backscatter in normal arteries is highly variable, and therefore, backscatter from the intima reflects this variability.

Finally, my suggestion regarding the technology is to concentrate on the procedures we already can do, for example, flow reserve in the arteries and gross morphology, and not to give priority to the more far-reaching, esoteric applications.

Dr. DeMaria: My response relates to the issue of reimbursement. In this era of outcomes research, if we say to a third-party provider that we want to use a Doppler measurement to determine if a patient should have an angioplasty, they will reply, "What is your evidence? Where is the double-blind, randomized, prospective study that proves a difference?" I think it may work, but we are a long way from demonstrating it, and an even longer way from being reimbursed for it.

Dr. Nathaniel Reicheck (Philadelphia, Pennsylvania): I would like to mention another side of the medical economics issue: the industry side. Companies have all witnessed circumstances where the investigation of innovative and interesting technology has died out because there has been no way to generate revenue from it. That is a major risk in this area. One potential short-term answer to this problem is the intraoperative application for epicardial imaging that Dr. Pandian discussed. It has really not been explored and has the potential for a fast and explosive impact in clinical practice every day in operating rooms throughout this country.

Dr. Pandian: If a device were available for intraoperative epicardial imaging that produced reasonably good resolution (it does not have to be as good as some of the 30 MHz transducers), I believe every coronary bypass surgeon would be using it to show disease. I think there is a clear role for epicardial imaging.

One other comment I would like to make is that while current research and future investigation should be guided by what will be clinically useful and cost effective, we also have to explore all possible applications and developments in ultrasound, including those that may not have direct or immediate utility.

Dr. DeMaria: I think the most interesting aspect of intravascular ultrasound is the study of the biology of atherosclerosis, but no one will pay us to simply do research. We must have a clinical application. Dr. Goldman also brought up a good point. The instrument companies are now selling products that, in one sense, are not quite finished. However, if they do not do this, research and development capital just is not forthcoming.

Dr. Appleton: The most immediate application of intravascular ultrasound is directional atherectomy, because restenosis is a major problem. If it could be shown that performing directional atherectomy of the plaque would make a difference in the incidence of restenosis, these catheters would be widely used. Collaborative studies would be beneficial in this area.

I think a regression study is important and would have a tremendous impact on clinical practice to demonstrate that vigorous treatment lowered cholesterol levels. It could also show that even the first part of the left anterior descending artery caused plaque regression. If it could be shown that regression is more easily done than previously thought, and it proved to be an important part of treatment, it would really change the way preventive cardiology is practiced in this country.

Would the panelists please update us on directional atherectomy and address what is being done peripherally? Are people cooperating through collaborative studies?

Dr. DeMaria: Regarding the collaborative and regression studies, at this stage we do not have data on reproducibility. We do not know if 2 investigators performing the same technique will arrive at the same conclusion, or if one person performing the same technique twice will arrive at the same answer. It is very difficult to design these protocols. How do you find a patient who is willing to undergo serial intracoronary ultrasound? I think we are several steps away from being able to provide a methodology that can detect a 10–15% regression.

It would be an enormously important contribution if some aspect of intravascular ultrasound could predict propensity to restenosis.

Dr. Grayburn: A year ago I spoke with Scott Gundy, a very well-known atherosclerosis specialist. We talked about doing a regression study with a patient population that has a very careful characterization of the lipid profiles. To my surprise no one was interested in funding the study, which I think would be extremely useful in terms of understanding the pathogenesis and treatment of atherosclerosis.

In terms of restenosis there is no doubt that intravascular ultrasound offers an opportunity to better direct the atherectomy and to achieve a more optimal result. As Dr. Nissen mentioned earlier, restenosis is often due to failing to get an appropriate result in the first place and just not recognizing the situation angiographically. In some cases the angiogram looks fine and one would consider the procedure a success. Then after the intravascular catheter is in place, it looks bad and you have to go back and do more work.

So I believe there is tremendous potential for the restenosis applications. Unfortunately, what we know is based solely on anecdotal experience. The data need to be established from a more collaborative effort.

Dr. Nissen: I am not quite so optimistic about directional atherectomy, because the current atherectomy devices are large and limited to just the first few centimeters of the coronary. If a technique is suitable for only 1% of all angioplasty, I am concerned that it may not ever become an optimal procedure.

There are a few cooperative studies and at least one claims that restenosis can be predicted based on plaque morphology. I admit to being skeptical, and I would like first to evaluate all the data, but it appears that several people are working with some centers around the country that have provided data on this subject.

Regarding regression, a study by Greg Brown showed there was a 2% change in the lumen diameter in the regressed patients and a 50% reduction in the event rate. How can that be explained? I wonder if this remodeling process does not work both ways: the plaque can push the outer wall of the vessel out, while the size of the lumen does not change significantly. It is possible to force lipid out of the plaque, and the wall can come back in again. Therefore, plaque bulk may be markedly reduced by regression without altering the lumen. Perhaps the angiographers are overlooking this possibility, but I think it must be addressed.

Dr. Pandian: In terms of atherectomy, I think guided directional atherectomy may provide better results, but I do not believe that the problem of restenosis will be eliminated. It is certain that lesion size after atherectomy is only one of many determinants of restenosis. There are other areas, but the problem is a lack of systematic data at the present time.

Regarding the multicenter studies, I know of 2 current studies, 1 of which includes data on the predictability of restenosis based on the basic ultrasound appearance. However, it is too early to draw conclusions, because there are no confirmed data. We will have to wait for results from future studies.

Concerning progression and regression, I believe 3-dimensional intravascular ultrasound imaging will be the only way to study these areas accurately. It may be too early now, but that is definitely the direction to take.

Dr. Weintraub: I agree with what has been said thus far. In addition, I would like to add that perhaps other mechanical interventions could be assisted by the intravascular ultrasound procedures that are currently in use. Although based strictly on anecdotal experience, the ability to assess the efficacy of stent deployment in a lesion can be assisted by intravascular ultrasound. Directional atherectomy can be assisted by intravascular ultrasound, but the restenosis issue is separate.

As to the cooperative trials, Tufts University has been involved in a few that identify the morphology of the atherosclerotic plaque. Again, I think it is very important to have clinical applications, either present or future, for what we see on intravascular ultrasound.

Dr. Goldman: I think plaque morphology, whether or not it is guided by ultrasound, may not tell us about restenosis. There is something distinct in the lesion and, whether we do angioplasty or atherectomy, there is a 30% restenosis rate, so there is a common link. It probably will require some manipulation of the biology of the recently damaged plaque, perhaps by local instillation of heparin, in order to change it. Part of the problem, because of the lack of data, is to go back and see a terrible-looking flap. What does it really mean?

Since we are looking at only a very small percentage of all the angioplasties performed, does that connote a worse long-term prognosis for restenosis?

Defining plaque morphology may not help us to determine our final procedure, but at least we are one step ahead. One cannot say that the proximal portion of the plaque we see is necessarily what was in the plaque before the angioplasty. I think that local thrombolytic instillation and local treatment should be assisted by the ultrasound device, once the angioplasty or atherectomy is performed.

It really is important for those of us here to become involved in cooperative studies. If we wait for companies to provide funding, it probably will not happen. It is up to us to take the initiative and say that this is something we want to pursue. If we combine our efforts, this approach may be much more productive toward persuading major ultrasound companies to become involved both investigatively and financially.

Dr. DeMaria: Let me ask the interventionalists on the panel a question. Is there any evidence showing that it is possible to predict the success rate of PTCA based on intravascular ultrasound? Is there anything about the plaque that would suggest that it will never dilate, and we should not even try to inflate the balloon?

Dr. Weintraub: No evidence that I know of.

Dr. DeMaria: Is that a potential? We know there are a number of plaques that just do not yield decent results, and, therefore, it is probably not worth risking a dissection.

Dr. Weintraub: The major problem, again, is identifying the lesion morphology and getting across the lesion before mechanical intervention.

Myocardial Perfusion: Contrast Echocardiography Perspectives

Steven B. Feinstein, MD

Contrast echocardiography may become a useful means of quantifying transmural regional myocardial perfusion patterns, experimentally and clinically, in a variety of settings. Contrast echocardiography has already been used in the operating room to study perfusion during coronary artery bypass graft (CABG) surgery. Other recent studies have demonstrated the ability of contrast echocardiography to predict wall motion improvement following acute myocardial infarction and therapeutic intervention. This is significant in the light of the discrepancy that has recently been shown between epicardial coronary vessel diameter and coronary flow. Studies suggest that both tissue and blood flow and volume may be quantitatively evaluated using contrast echocardiography, and these parameters ultimately may be used to assess tissue viability or vascular reserve. Contrast echocardiography techniques have been shown to be safe and reliable, and provide a high degree of spatial and temporal resolution.

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When we discuss myocardial perfusion, consider the fact that today, when nitroglycerin is given to a patient with angina, the angina is often relieved, yet we do not have a complete understanding of the underlying physiologic reason this occurs. In order to study the physiologic effects of a pharmaceutical therapy such as nitroglycerin, we need to examine myocardial perfusion; however, until now we have had no readily available clinical means for directly evaluating transmural blood flow. Although flow reserve measurements provide a qualitative clinical indication of perfusion, contrast echocardiography may, with further development, be useful in actually quantitating regional tissue perfusion. This may require the development and refinement of ultrasound hardware and software that will permit more sensitive detection of the microbubbles within the myocardial tissue and the display of a broader range of reflected ultrasound data.

The following discussion begins with a brief history of contrast echocardiography, and then highlights the development of contrast agents, current clinical applications, and experimental issues that are the focus of current investigations.

HISTORICAL PERSPECTIVE

Contrast ultrasound may have had its earliest beginnings with the observations of Joyner, who, it is believed, observed the strong reflectant effect of microbubbles on the reflected ultrasound beam. In 1968, Gramiak and Shah[1] published their observation of a contrast effect following intracardiac injections of agitated indocyanine green, which contained suspended air-filled microbubbles. These observations occurred during a cardiac catheterization procedure while the heart was being simultaneously scanned using echocardiography. Following this report, contrast echocardiography was used by Feigenbaum et al[2] for left ventricular cavity identification, by Kerber et al[3] to detect and highlight valvular regurgitation, and by Sahn and Valdez-Cruz[4] to assess intracardiac shunts.

The first use of ultrasound contrast agents to

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image myocardial perfusion directly was performed by DeMaria et al.[5] This group studied the regional perfusion patterns produced by direct injections of microbubbles into the coronary arteries. DeMaria's group was among the first to describe the need to calibrate the ultrasound reflection and bubble concentration and to apply dye dilution theory for quantitation of the contrast echocardiographic effect.[6] Following these early reports describing the use of contrast echocardiography to study myocardial perfusion, Tei et al[7] and Armstrong et al[8] independently reported the reproducibility of these methods. A "gold standard" for comparing and validating contrast echocardiographic techniques was later developed by Kaul et al,[9] who observed that perfusion deficits defined by contrast echocardiography were comparable in area to those defined by nuclear imaging techniques.

The first use of contrast echocardiographic techniques in the operating room for the purpose of studying perfusion in patients undergoing coronary artery bypass graft surgery was reported by Goldman et al.[10] More recently, the safety and efficacy of a commercially prepared, intravenous contrast agent was reported in a multicenter clinical trial.[11]

DEVELOPMENT OF CONTRAST AGENTS

The earliest ultrasound contrast agents were produced by manual agitation or hand shaking of a liquid such as saline, dextrose or Renografin-76. This shaking generated air bubbles that would serve as echo reflectors. However, it was observed that these manually prepared bubbles were variable in size and in persistence. Therefore, the potential for air emboli existed. Further, due to their relatively large size and transient nature, the microbubbles were not useful for visualizing left heart structures following intravenous injections. However, it was generally believed that smaller microbubbles, measuring <25% of the ultrasound beam wavelength, would not be sufficiently echo reflective.[12]

That theory was disproved by the subsequent use of a mechanical sonicator to create smaller microbubbles. The smaller sonicated microbubbles were effective ultrasound reflectors, despite the fact that the bubbles were physically smaller than what was thought to be the resolving power of the ultrasound wavelength. In addition, the sonicated bubbles were found to be more stable and uniform in size than the earlier hand-agitated microbubbles.[13] Once a standardized contrast agent was developed, the next logical step was to begin efforts at quantifying the contrast effect.

The first reported effort at quantitation of the ultrasound contrast effect was described by DeMaria et al.[14] The authors showed that cardiac output could be correlated to a videodensitometric time–intensity curve following the loss of contrast effect (or indicator) within the left ventricular cavity. Using similar videodensitometric methods of analysis, significant experimental and clinical progress has been made in attempting to quantify regional myocardial perfusion using contrast echocardiographic techniques.[15] With these advances, it is now possible to approach the problems of myocardial perfusion imaging in patients having coronary artery disease.

CURRENT AND FUTURE CLINICAL APPLICATIONS

Recent studies have shown that coronary anatomy (as defined by angiography) may not adequately indicate myocardial perfusion or tissue viability. Today, a primary clinical issue is the relation between coronary anatomy and myocardial perfusion. To illustrate this point, Figure 1 was prepared after the report by White et al[16] highlighting the discrepancy between epicardial coronary vessel diameter and coronary flow. To illustrate further the differences between coronary anatomy and physiology, Ito et al[17] have recently shown that the degree of wall motion improvement following an acute myocardial infarction and therapeutic intervention was prospectively predicted by contrast echocardiography but was not predicted by coronary angiography. Although this result was anticipated from experimental animal studies, Ito et al[17] were the first to apply contrast echocardiographic techniques to predict human tissue viability and function.

These studies show that myocardial perfusion and epicardial coronary anatomy are not interchangeable as markers for predicting tissue viability. This is illustrated symbolically in Figure 1, where the "branches of the tree" represent coronary anatomy and the "leaves of the tree" represent tissue perfusion. As can be seen in this diagram, the tree may have "normal" branches but no leaves (indicating no perfusion), even when the underperfused branch otherwise appears to be normal. Although considerably more complex, the coronary anatomy of a patient may appear to be normal and yet may not have normal or adequate myocardial perfusion. The converse may also be true; that is, one may have abnormal coronary

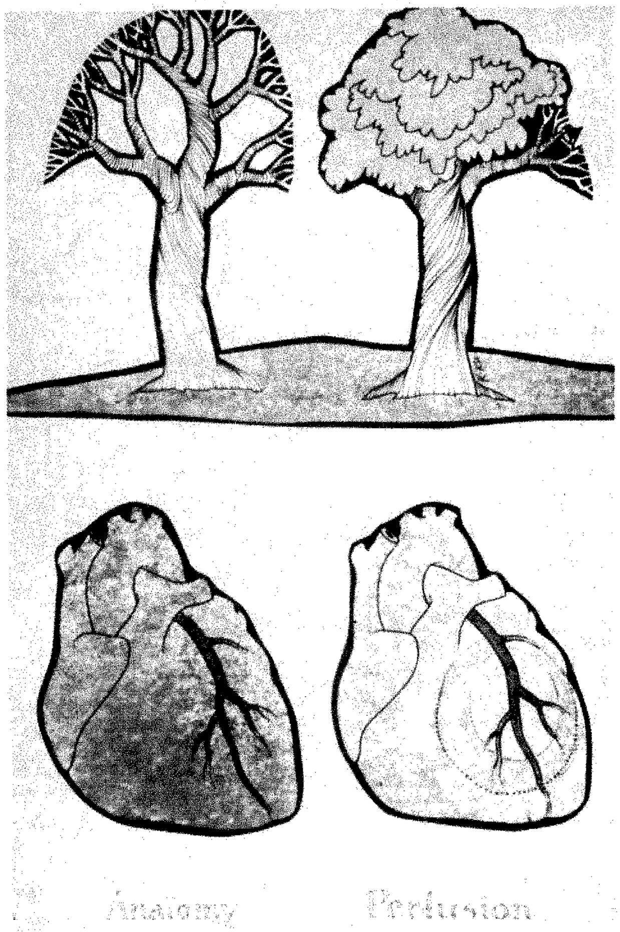

FIGURE 1. This schematic diagram represents the apparent differences between anatomy and perfusion. In the tree model, it is observed that the anatomy (branch) may be intact—yet the perfusion is lacking. By comparison in the heart model, it is possible to have abnormal coronary anatomy and yet the degree of myocardial perfusion may remain unknown.

anatomy (coronary stenoses or occlusions) and yet maintain adequate perfusion. Because the human coronary anatomy, as assessed by angiography, has not been shown to predict the myocardial perfusion pattern uniformly, the use of contrast echocardiography as a perfusion marker may now play a significant role in the management of patients having ischemic heart disease.

Moreover, in addition to quantifying total regional myocardial perfusion, contrast echocardiography may permit the quantitaion of transmural regional myocardial perfusion patterns. The ability to "dissect" out the regional perfusion patterns of the myocardium is important because the flow patterns of the subendocardial and subepicardial regions do not necessarily parallel each other.[18]

Recent clinical reports indicate that it may become routine to assess both anatomy and perfusion of the myocardial tissue during coronary arteriography. However, in humans, regional perfusion defects may be quite heterogeneous. The use of contrast echocardiographic techniques may distinguish viable from nonviable tissue. The Figure 2 demonstrates the variation of tissue viability following an acute coronary occlusion. Note that discrete areas of fibrosis exist within regions of relatively preserved tissue. If this patient had had hypertensive heart disease, a previous myocardial infarction, coronary artery bypass graft, or a combination of these, it would be exceedingly difficult to predict the extent of the defect area based solely on epicardial vessel anatomy. It is anticipated that in humans, similar to prior experimental studies, regions of low flow or no-flow (fibrosis, acute

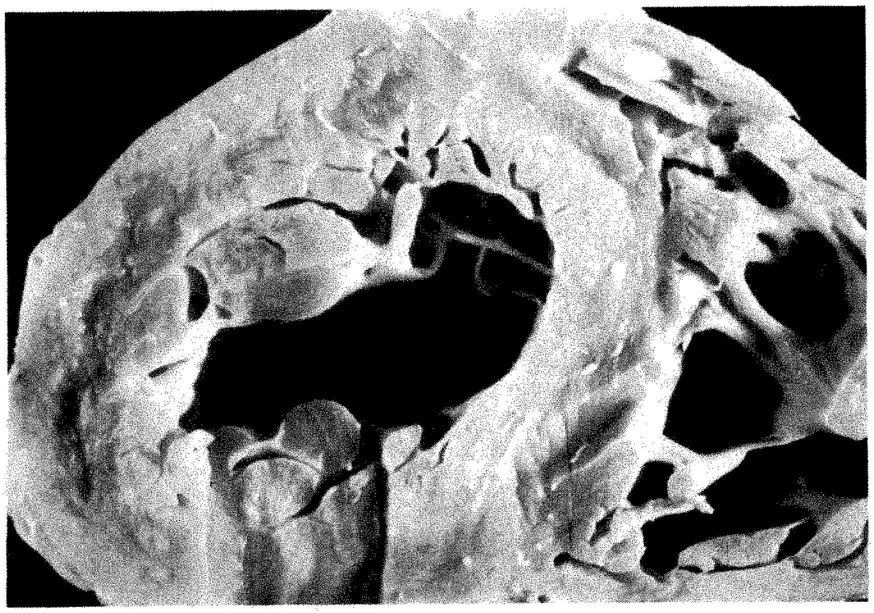

FIGURE 2. Cross-sectional view of the myocardium. In this specimen it is possible to see "islands" of fibrosis (white areas) intermingled with viable tissue. From this example, it is apparent that the ability to predict viable myocardial tissue requires an imaging system with a high degree of spatial resolution.

occlusion, or infarction) are not perfused with a significant quantity of ultrasound contrast tracers (microbubbles). Therefore, these regions can be clearly identified from "normal" perfusion areas with the use of contrast echocardiography.

Currently, the technology associated with contrast echocardiography has the spatial and temporal resolution to detect transmural differences between perfused and infarcted tissue. However, several clinical issues pertaining to regional perfusion remain open for investigation. For example, what happens to the transmural blood volume during the cardiac cycle? Or in hypertensive patients? Or in a patient with ischemia? To begin to answer these questions, further studies need to be performed in the clinical arena.

CURRENT EXPERIMENTAL RESEARCH ISSUES

Tissue perfusion is interrelated with tissue blood flow and volume. These factors appear to co-vary and may be independently studied using mathematical approaches. Figure 3 reveals 3 experimental conditions that illustrate the effect of altering tissue blood volume and flow in an intact canine model. Three experimental conditions were developed: (1) control or resting state, (2) steady state following an intracoronary infusion of adenosine, and (3) normocapnia–hypoxic state. The animal

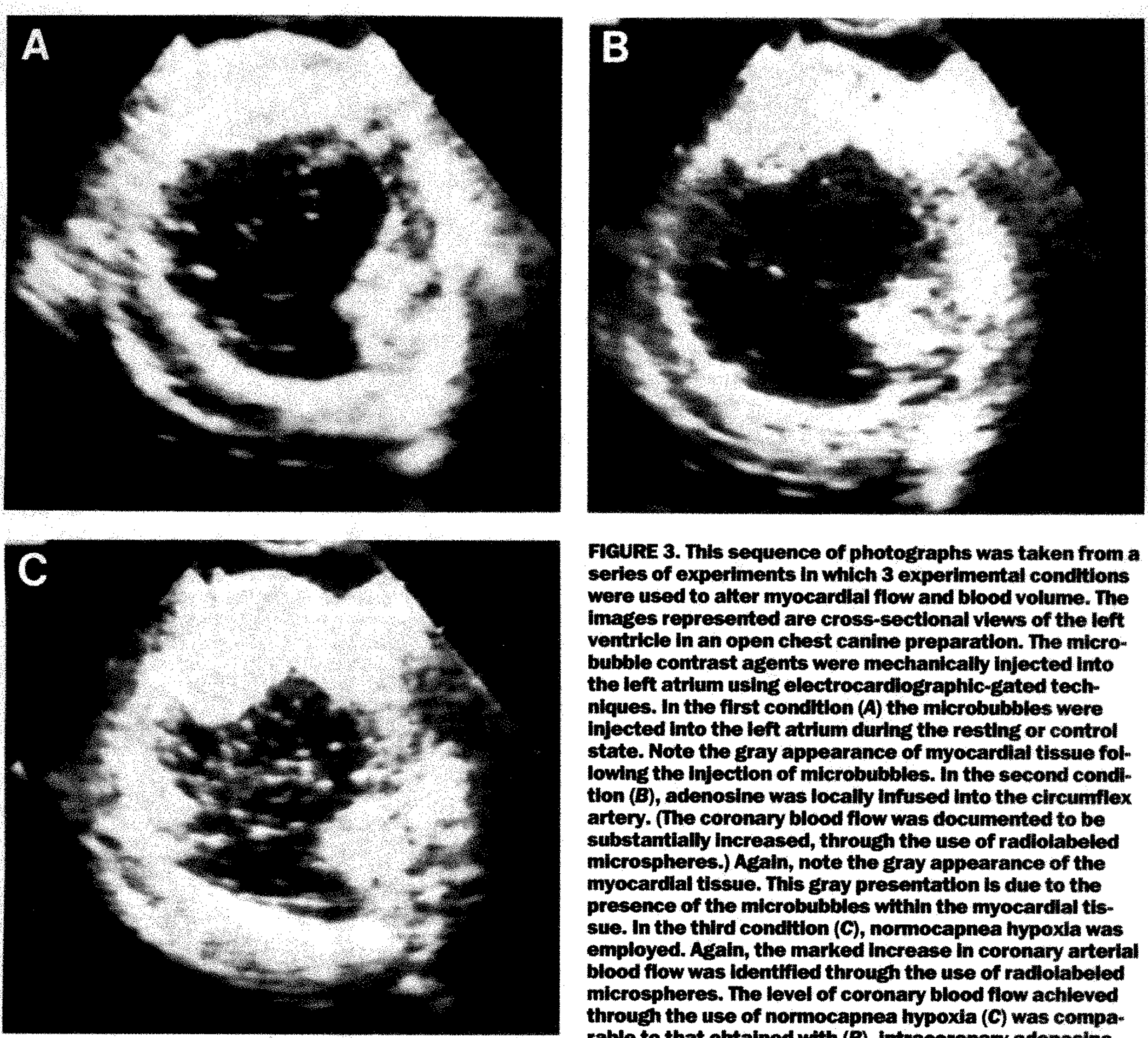

FIGURE 3. This sequence of photographs was taken from a series of experiments in which 3 experimental conditions were used to alter myocardial flow and blood volume. The images represented are cross-sectional views of the left ventricle in an open chest canine preparation. The microbubble contrast agents were mechanically injected into the left atrium using electrocardiographic-gated techniques. In the first condition (*A*) the microbubbles were injected into the left atrium during the resting or control state. Note the gray appearance of myocardial tissue following the injection of microbubbles. In the second condition (*B*), adenosine was locally infused into the circumflex artery. (The coronary blood flow was documented to be substantially increased, through the use of radiolabeled microspheres.) Again, note the gray appearance of the myocardial tissue. This gray presentation is due to the presence of the microbubbles within the myocardial tissue. In the third condition (*C*), normocapnea hypoxia was employed. Again, the marked increase in coronary arterial blood flow was identified through the use of radiolabeled microspheres. The level of coronary blood flow achieved through the use of normocapnea hypoxia (*C*) was comparable to that obtained with (*B*), intracoronary adenosine. However, the appearance of the contrast effect noted in the muscle is considerably different from that noted in the adenosine condition, despite the fact that the coronary *blood flow* was the same as measured by radiolabeled microspheres. An explanation for the observed differences noted may be attributed to changes in tissue blood volume during hypoxia. If the blood volume in the muscle is increased, the peak intensity of the ultrasound contrast effect will also be increased due to the increased quantity of an indicator within the tissue. These studies, through the use of contrast echocardiography, highlight the differences between blood flow and tissue blood volume.

heart was imaged using a 2-dimensional echocardiogram and a cross-sectional image was obtained. The afferent coronary flow to the myocardium was measured using standard radiolabeled microspheres.

Data from these studies revealed that the arterial flow was increased to the same degree in both the adenosine and hypoxic conditions. However, it was clear from the still-frame ultrasound images of the heart that these conditions did not result in the same observed contrast effect. The hypoxic condition had a "brighter" image (consistent with increased tissue blood volume) than either the adenosine or control states. Thus, this experiment highlighted and identified the significant differences between blood flow and myocardial blood volume. That is, although the adenosine condition and the hypoxic state were noted to have similarly increased arterial flow to the heart, the ultrasound contrast effect noted in the myocardium was significantly different.[19] Despite nearly identical arterial flow rates, one explanation for the different appearance of the contrast effect may be the marked changes in microvascular blood volume associated with hypoxia. Although flow and volume may co-vary in the same tissue, it is not adequate simply to use methods that detect only flow (in this case, the use of radiolabeled microspheres) while ignoring the tissue volume status. It is possible that through the use of contrast echocardiography it may become possible to quantitate both tissue flow and blood volume, in which case these parameters ultimately may be used to assess tissue viability and vascular reserve.

In an effort to quantify myocardial perfusion, our laboratory has developed a mathematical formula for calculating both flow and volume based on classic dye dilution principles.[20] Using videodensitometric techniques, we can generate time–intensity curves (Figure 4). From these curves, we derive multiple analysis parameters (i.e., area under the curve, peak intensity, tissue transit time, etc.). These derived parameters are then used to determine tissue blood flow and volume. This particular mathematical model has been tested in vitro in our laboratory and is currently undergoing in vivo testing as well. Our results to date reveal that we are able to calculate flow directly based on these carefully controlled studies in the animal laboratory.

Similarly, our laboratory is now developing validation techniques to quantitate contrast echocardiographic data by directly assessing the microvascular blood volume and flow based on previously validated techniques.[21] This ongoing validation work is important in establishing a basis from which to derive tissue perfusion parameters in the future.

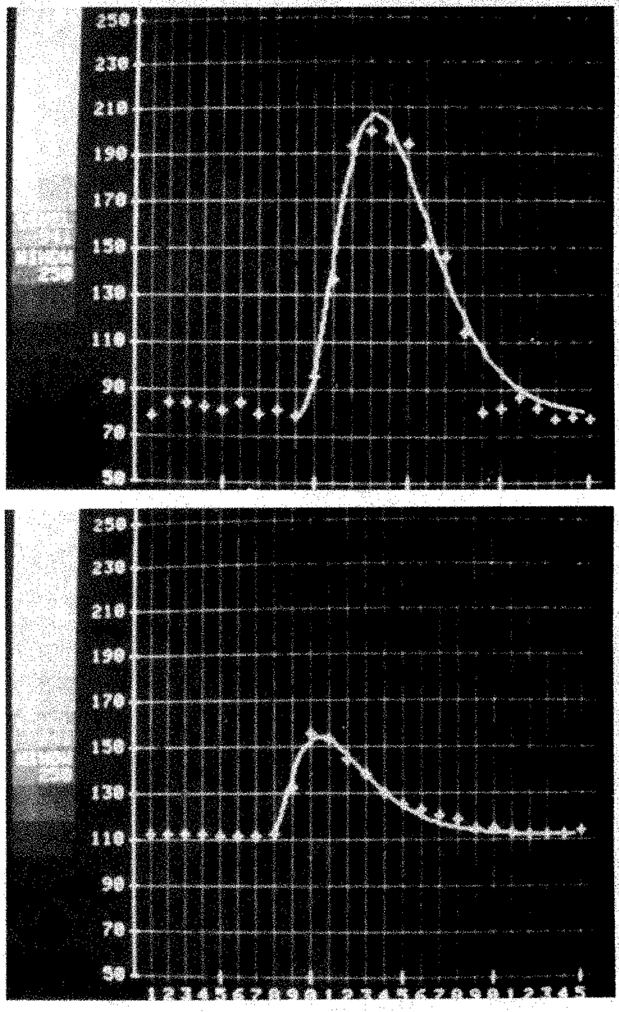

FIGURE 4. These 2 videodensitometric time–intensity curves represent the appearance and disappearance of the contrast material as it passed beneath the ultrasound beam in the descending aorta and in the kidney parenchyma. The ordinate is the pixel intensity of the contrast effect (digitized from videotape recordings) and the abscissa is time in seconds. Note, the first graph (top, descending aorta) reveals a higher peak intensity and a shorter total transit time. The second graph (bottom, kidney parenchyma) demonstrates the perfusion characteristics of the target organ. Due to the fact that the kidney is downstream of the input regions (aorta) the peak intensity is less and the total transit time is longer. From these 2 curves, it may be possible to calculate, both tissue blood flow and volume.

CONCLUSION

Contrast echocardiographic techniques provide a safe, reliable, and sophisticated method of measuring tissue perfusion with a high degree of spatial and temporal resolution. The heterogeneity of regional myocardial blood flow and volume (including endocardial and epicardial differences) may now be investigated using contrast echocardiography during coronary arteriography and cardiac surgery and potentially in the outpatient clinic setting. Ongoing development of mathematical approaches to quantitation of blood flow and volume will require further validation and clinical testing. This work promises to produce a reliable method of quantifying regional myocardial perfusion in experimental and clinical settings. This in turn may permit physicians to evaluate the viability of tissue in order to consider preventive measures and the efficacy of pharmaceutical or other interventions.

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Sonicated Serum Albumin in Contrast Echocardiography: Improved Segmental Wall Motion Depiction and Implications for Stress Echocardiography

Linda J. Crouse, MD

We undertook to study the ability of intravenously administered sonicated albumin microbubbles to opacify the left ventricular (LV) cavity, enhance endocardial delineation, and thereby improve the interpreter's confidence in evaluating regional wall motion in patients whose baseline echocardiograms were believed to be technically difficult because of limited endocardial resolution. We studied 30 adult patients with endocardial border dropout of ≥20% on routine echocardiography. Efficacy was evaluated by the investigator and 2 blinded observers using an opacification grading system of 0 (no appearance in LV cavity) to 3+ (full LV chamber opacification). Effective opacification was indicated by a score of ≥2+. Border delineation improvement equaled a change from grade A (not well delineated) to grade B, C, or D (well delineated) of at least 1 of 6 LV wall segments. Initially all patients received a 0.08 mL/kg injection. The patient received 2 additional injections of 0.14 and 0.08 mL/kg given 5 minutes apart if the initial volume produced at least 2+ LV opacification. Otherwise, a final injection of 0.22 mL/kg was given. In all cases, the patients' arms were raised after injection to enhance venous passage.When graded by the investigator, 29 patients (97%) exhibited ≥2+ opacification. When graded by the blinded observers, 27 patients (90%) exhibited ≥2+ opacification. Improved border delineation was noted by the investigator in 90% of patients, and the blinded observers noted improvement in 97% (excluding 1 patient who, if scored by a blinded observer, would have received a higher dose of contrast agents). Confidence in assessing LV wall motion improved in 24 (80%) of the 30 patients studied. Whereas results of routine echocardiography may be inconclusive because of suboptimal endocardial border delineation, intravenous administration of sonicated albumin microbubbles improves border delineation and promotes the confidence of the investigator in assessing wall motion.

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Exercise echocardiography has shown great promise in the evaluation of patients with known or suspected coronary artery disease. It has been shown to be superior to exercise electrocardiography and comparable to, if not superior to, exercise thallium scintigraphy and radioventriculography in assessing patients in various subgroups.[1]

We have accumulated a very large experience with stress echocardiography as a screening test for coronary artery disease and in the evaluation of patients who have had previous coronary angioplasty, coronary bypass surgery, or myocardial infarction. Based on our experience, we believe that stress echocardiography, even in technically difficult patients, is the noninvasive diagnostic test of choice in many of these patient populations. In speaking with physicians around the country about the applicability of stress echocardiography, it is clear that the major limitation impeding its rapid and widespread acceptance and clinical applications is the widely held belief that regional wall motion analysis is very often limited by technically inadequate echocardiograms, owing to endocardial dropout.

It would appear that any method that would enhance the interpreters' ability to assess regional left ventricular (LV) wall motion would enhance the acceptability of this test. Despite the introduc-

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tion of a variety of technologic enhancements of echocardiographic apparatus, there appears to be an irreducible number of patients, which approaches 10% in several large reported series, in whom echocardiographic analysis of regional wall motion is considered to be technically difficult.[2]

Enhanced endocardial depiction through any means should allow for improved echocardiographic evaluations of regional wall motion. Contrast echocardiography has been used to: (1) measure cardiac output,[3] (2) evaluate cardiac valve repair,[4] and (3) detect defects in cardiac function or anatomy.[5–8] The use of sonicated albumin microbubbles has been shown to opacify the left ventricle in a large majority of patients and thereby enhance delineation of the endocardial–cavitary interface.[8,9]

We undertook to study the ability of intravenously administered sonicated albumin microbubbles to opacify the LV cavity, enhance endocardial delineation, and thereby improve the interpreter's confidence in evaluation of regional wall motion in patients whose baseline echocardiograms were believed to be technically difficult because of limited endocardial resolution.

METHODS

Patients who exhibited ≥20% loss of delineation of the endocardial border on routine echocardiography were asked to participate. Thirty patients were enrolled, 12 women and 18 men, age 26–76 years (mean 56 years). Exclusion criteria included: (1) pregnancy; (2) lactation; (3) history of blood product hypersensitivity; (4) inability to follow instructions or mental incompetence; and (5) routine echocardiograms in which basic cardiac structures could not be imaged.[10]

Two or 3 injections of human serum albumin were given to patients with inadequate endocardial border delineation on routine echocardiography. Using a decision tree based on the echocardiographic contrast rate following the first injection, patients were assigned to a 2-injection or 3-injection group. The opacification grading system used grades 0 to 3+. A score of 0 equaled no contrast, and a score of 3+ indicated full opacification of the left ventricle. Effective opacification was indicated by a score of ≥2+.[10]

The initial dose administered to all patients was 0.08 mL/kg body weight. If intermediate (≥2+) LV opacification was observed following this intravenous dose, then a second dose of 0.14 mL/kg was administered. Patients who received a third dose were again injected with 0.08 mL/kg. Echocardiographic imaging was performed for 2–3 minutes following each dose to ensure that echocardiographic contrast had cleared from the ventricle before the subsequent dose. The interval between doses was approximately 5 minutes.

If the initial injection did not produce intermediate or greater LV opacification, the patient received a large second bolus of 0.22 mL/kg. Thus, all patients received a total of 0.3 mL/kg of sonicated albumin microbubbles in either 2 or 3 individual doses. In all cases, patients' arms were raised immediately after each injection to enhance venous passage.[10]

Each patient was also examined after each injection, using standard echocardiographic equipment with the patient in the left lateral decubitus or supine position, in addition to the initial routine 2-dimensional echocardiographic study. The study was recorded continuously on videotape. The ultrasound studies were adjusted initially for optimal endocardial visualization and were not readjusted.[10]

According to the described grading system, the recorded images were evaluated for contrast opacification and improved endocardial border delineation by the investigator and 2 independent blinded observers. Images were recorded in an apical 4-chamber view in 25 patients (83%) and an apical 2-chamber view in 5 patients (17%).[10]

Opacification was graded on a scale from 0 (no appearance in LV cavity) to 3+ (full LV chamber opacification). In addition, the left ventricle was divided into 6 segments in the apical 2- or 4-chamber view.[10]

The endocardial definition in each segment was rated on a scale from A (not well-delineated) to D (well-delineated). Improved LV opacification was judged if there was ≥2+ opacification, and improved endocardial border delineation was defined as an improvement from grade A to grade B, C, or D of at least 1 of the 6 LV wall segments.[10]

Each study was interpreted by the investigator. Videotapes of each study were sent to 2 blinded observers for separate considerations. Results of all 30 patients were reviewed as reported below, with 1 exception. In the 3-injection group, technical malfunctions resulted in lost studies of the second injection in 1 patient.[10]

Safety was monitored prestudy and 30 minutes poststudy for vital signs, electrocardiograms, blood pressures, respiratory rates, and heart rates. Patients were also contacted by telephone 24 hours

TABLE I Average Opacification Grades in Good Responders* after Three Injections of Sonicated Serum Albumin

	Volume Administered (mL/kg)		
	0.08	0.14	0.08
Opacification grade	2.35	2.71	2.73

*First response ≥2+.
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TABLE III Improved Border Delineation After Three Injections of Sonicated Serum Albumin

	Volume Administered (mL/kg)		
	0.08	0.14	0.08
Investigator reviewed*			
Yes	18 (90%)	18 (95)%	20 (100%)
No	2 (10%)	1 (5%)	0 (0%)
Total	20	19	20
Blinded observers*			
Yes	19 (95%)	19 (100%)	20 (100%)
No	1 (5%)	0 (0%)	0 (0%)
Total	20	19	20

*Due to instrument malfunction, data for second injection in patient 16 is missing.
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TABLE V Acceptable Opacification After Two Injections of Sonicated Serum Albumin

	Volume Administered (mL/kg)	
	0.08	0.22
Investigator reviewed		
Yes	0 (0%)	9 (90%)
No	10 (100%)	1 (10%)
Total	10	10
Blinded observers		
Yes	3 (30%)	7 (70%)
No	7 (70%)	3 (30%)
Total	10	10

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TABLE II Acceptable Opacification After Each Injection of Sonicated Serum Albumin

	Volume Administered (mL/kg)		
	0.08	0.14	0.08
Investigator reviewed*			
Yes	20 (100%)	19 (100)%)	19 (95%)
No	0 (0%)	0 (0%)	1 (5%)
Total	20	19	20
Blinded observers*			
Yes	19 (95%)	19 (100%)	19 (95%)
No	1 (5%)	0 (0%)	1 (5%)
Total	20	19	20

*Due to instrument malfunction, data for second injection in patient 16 is missing.
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TABLE IV Average Opacification Grades in Poor Responders* After Two Injections of Sonicated Serum Albumin

	Volume Administered (mL/kg)	
	0.08	0.22
Opacification grade	1.15	2.15

*First response ≤2+.
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TABLE VI Improved Border Delineation After Two Injections of Sonicated Serum Albumin

	Volume Administered (mL/kg)	
	0.08	0.22
Investigator reviewed		
Yes	1 (10%)	7 (70%)
No	9 (90%)	3 (30%)
Total	10	10
Blinded observers		
Yes	5 (50%)	9 (90%)
No	5 (50%)	1 (10%)
Total	10	10

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poststudy to complete a follow-up questionnaire and to assess any adverse effects.[10]

Throughout the study, the major adverse effect was abnormal taste sensation which was an insignificant finding. No medically significant side effects were observed.[10]

The investigator and blinded observers measured efficacy by assessing the degree of contrast opacification in the cardiac chambers according to the following grades: (1) 0 signifies no opacification; (2) 1+ signifies faint opacification; (3) 1.5+ signifies faint to intermediate opacification; (4) 2+ signifies intermediate to full opacification, and (5) 3+ signifies full chamber opacification. If at least 1 baseline grade A segment (not well-delineated) improved to a grade B, C, or D (well delineated) after the administration, then border delineation was considered efficacious.[10]

The blinded observers were not informed of the order or volume of the human serum injections. Tapes were also randomly reviewed.[10]

The contrast agent used was Albunex, a brand of sonicated human serum albumin in a sterile, nonpyrogenic aqueous solution. Sonication of the 5% human albumin solution results in the formation of air-filled albumin microbubbles with an average diameter of 4 μm.[10]

RESULTS

Following the initial 0.08 mL/kg injection of the contrast agent, the investigator deemed 20 (67%) of the 30 patients studied to have an acceptable

(≥2+) degree of opacification. These good responders became the 3-injection group. Table I shows the investigator-rated opacification grades following each injection in this group.[10]

Table II shows data on good responders who had acceptable opacification grades after each injection, as graded by the investigator and blinded observers.[10]

Table III shows judgments of improvement by both the investigator and the blinded observers in border delineation in the good responder group following each injection.[10]

The investigator concluded that 10 (33%) of the 30 patients studied failed to show an adequate opacification response to the initial 0.08 mL/kg injection. Tables IV – VI show the results of their studies. Of this group, 70% showed acceptable opacification following the second injection of contrast agent (0.22 mL/kg).[10]

DISCUSSION

This study provides important insight into the potential applications of intravenously administered echocardiographic contrast material in the very patients in whom echocardiographic analysis of regional wall motion is most difficult. Although a variety of echocardiographic contrast agents have been studied, most of these require intra-arterial or intraventricular administration in order to assure their appearance in the left heart.

Albunex is a stable suspension of air-filled albumin microbubbles created by sonicating a 5% solution of human serum albumin. Its ease of administration, high frequency of enhanced endocardial definition, and its ability to assess regional and global LV contraction have important potential implications.

Such enhanced endocardial definition will undoubtedly make stress echocardiography a more attractive diagnostic tool. It is hoped that the results from this trial will help overcome the widely held perception that regional wall motion analysis is difficult in a large minority of patients. The administration of human serum albumin allowed echocardiography to be applied even to patients who had been considered technically poor candidates for echocardiographic evaluation.

As computer technology evolves, automatic edge detection programs may also be able to depict, analyze, and score LV regional wall motion. The potential application of this technology to stress echocardiography can only be enhanced by the ability of contrast-enhanced endocardial depiction to assist not only the human eye but automated detection software as well.

CONCLUSION

We believe that regional wall motion analysis at rest and following cardiac stress is an invaluable tool in assessing known or suspected coronary insufficiency in many patient groups. A widespread acceptance of stress echocardiography has been hindered by the perception that regional wall motion is often difficult to assess because of limited endocardial definition.

The data accumulated from this trial clearly indicate that, in patients whose baseline echocardiograms are technically limited because of endocardial dropout, a contrast agent such as sonicated albumin microbubbles very often enhances LV chamber opacifications and segmental endocardial definitions, thereby enhancing the interpreter's confidence in evaluating regional wall motion.

Areas for future investigation include evaluation of myocardial perfusion using intra-arterial or intravenous administration of contrast material. The specific role of sonicated serum albumin as a contrast agent in conjunction with stress testing and its use in myocardial perfusion represent fertile ground for future clinical investigations.

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Clinical Applications of Myocardial Contrast Echocardiography

Sanjiv Kaul, MD

Myocardial contrast echocardiography is a new technique that uses microbubbles of air in conjunction with simultaneously performed 2-dimensional echocardiographic imaging. Currently, it can be used to determine myocardial perfusion in the cardiac catheterization laboratory and the operating room. For myocardial contrast echocardiography to find a broader clinical application for the assessment of myocardial perfusion, it will be necessary to opacify the myocardium from venous injection of contrast in humans. In this regard, enhancement in bubble engineering, optimization of echocardiographic systems (greater sensitivity and dynamic range), and availability of digital image enhancement techniques will be required for myocardial contrast echocardiography to realize its full clinical potential by the year 2000.

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Myocardial contrast echocardiography is an evolving technique that can be used to assess myocardial perfusion in vivo. It uses the intravascular injection of microbubbles of air, which produce contrast enhancement when passing through the myocardium during simultaneously performed 2-dimensional echocardiography. This technique has been validated in the canine model for assessing the size of risk area during coronary occlusion [1–4] as well as collateral blood flow within an ischemic bed.[5–7] The transit rates of the microbubbles through the myocardium have also been correlated in experimental conditions with regional myocardial blood flow.[8,9] More recently, myocardial contrast echocardiography has been applied increasingly in the clinical setting. This review will discuss the clinical applications of this technique in the 1990s and the potential clinical applications by the year 2000.

The most commonly used contrast agent in the clinical setting is sonicated Renografin-76, which consists of microbubbles with a mean diameter of 6–12 μm.[10,11] The intra-arterial injection of this agent has been found to be safe in humans, producing only transient changes in left ventricular (LV) and systemic hemodynamics.[12,13] These changes can be attributed to the hyperosmolality and calcium chelating properties of Renografin-76 itself rather than the introduction of microbubbles of air.

Sonicated albumin is also being increasingly used in the clinical setting.[14,15] The mean size of these bubbles is 4–5 μm. Being iso-osmolar and chemically inert, albumin microbubbles have no adverse effects on coronary blood flow or LV and systemic hemodynamics.[11,14] Moreover, these microbubbles have been shown to have an intravascular rheology that is similar to that of red blood cells,[16] making them ideal blood flow tracers. These microbubbles are now being commercially produced and are undergoing clinical testing.[17,18] Other contrast agents containing microbubbles of air are also being commercially produced and should be available for clinical use in the next few years.[19,20]

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TABLE I Clinical Applications of Myocardial Contrast Echocardiography in the 1990s

In the cardiac catheterization laboratory

- Assessment of risk area during coronary occlusion
- Assessment of infarct size following reperfusion
- Assessment of collateral blood flow
- Assessment of myocardial viability
- Assessment of coronary blood flow reserve
- Assessment of the success of coronary angioplasty

In the operating room

- Determination of route and adequacy of cardioplegia delivery
- Determination of sequence of graft placement
- Determination of success of graft placement

CLINICAL APPLICATIONS OF MYOCARDIAL CONTRAST ECHOCARDIOGRAPHY IN THE 1990s

The current clinical applications of myocardial contrast echocardiography require intra-arterial injection of contrast medium in the cardiac catheterization laboratory or in the operating room and are listed in Table I. Some of the increasing uses of myocardial contrast echocardiography in the cardiac catheterization laboratory will be discussed here.

Assessment of risk area during coronary occlusion: When a coronary artery is suddenly occluded, the region not receiving adequate blood flow and, therefore, likely to undergo necrosis, is termed the risk area.[21,22] Risk area can be defined on myocardial contrast echocardiography by injecting contrast medium proximal to a coronary occlusion. [1,2,4,23] Figure 1 is an example of a patient with an occluded left anterior descending coronary artery in whom contrast medium was injected first into the right coronary artery (panel A) and then into the left main artery (panel B). The region not showing any contrast during injection of either artery represents the risk area. Since the size of the risk area is the most important determinant of infarct size, its assessment in the clinical setting can help define management strategies during acute coronary occlusion.

Assessment of infarct size following reperfusion: Figure 2 is a short-axis view following left main artery injection of contrast medium after successful angioplasty of the left anterior descending artery in the same patient whose data are shown in Figure 1. A confluent region with "no reflow" is noted in the previously occluded bed. The area with "no reflow" correlates closely with infarct size in the animal model of coronary occlusion and reperfusion[24] and is caused by microcirculatory damage within the infarct zone.[25] Figure 3 is an example of data from one such animal; the top left panel is a contrast echocardiogram during coronary occlusion showing a risk area that corresponds well to that shown on postmortem autoradiography (bottom left panel). After reperfusion, contrast echocardiography shows a smaller area of hypoperfusion (top right panel) that corresponds to infarct size on postmortem staining of the heart with triphenyltetrazolium chloride (bottom right panel). It has recently been demonstrated that patients with large regions of no reflow on myocardial contrast echocardiography after attempted reperfusion in the early hours following acute myocardial infarction have poor LV function and short-term outcome.[26]

Assessment of collateral blood flow: It is apparent from Figure 1 that a large portion of the left anterior descending artery bed (shown by arrows) is perfused from the right coronary artery, since this area lights up after injection of contrast medium selectively into that artery. This patient demonstrated poor right-to-left collaterals on angiography. That myocardial contrast echocardiography is superior to angiography for demonstration of collateral flow should not be surprising. Coronary angiography can only define vessels >100 μm in diameter,[27] and most collateral vessels are smaller.[28] Further, the presence of an epicardial conduit on angiography does not define the extent of myocardial perfusion. Myocardial contrast echocardiography has been shown to be a superior technique for defining collateral blood flow both in patients with occluded[29] and nonoccluded vessels[30] and in those with recent[29] as well as remote myocardial infarction.[31] Interestingly, all studies using this technique have reported abundant collateral blood flow in patients with chronic coronary artery disease. As can be appreciated from Figures 1 and 2, regions supplied by collateral flow prior to reperfusion do not show the "no reflow" phenomenon after reperfusion.[29] Similarly, infarct sizes are smaller in patients with recent myocardial infarction who have abundant collateral flow by myocardial contrast echocardiography.[29]

Assessment of myocardial availability: Since collateral flow is abundant in patients with chronic coronary artery disease, it has been hypothesized that those with adequate collateral flow within an infarct zone will improve regional function after attempted angioplasty. In one study, patients with successful angioplasty of their vessel at a mean of 12 days after angioplasty were divided into two groups: those in whom $<50\%$ of the infarct zone was supplied by collateral flow and those in whom $\geq 50\%$ of the infarct zone was supplied by such flow. The latter group showed far better improve-

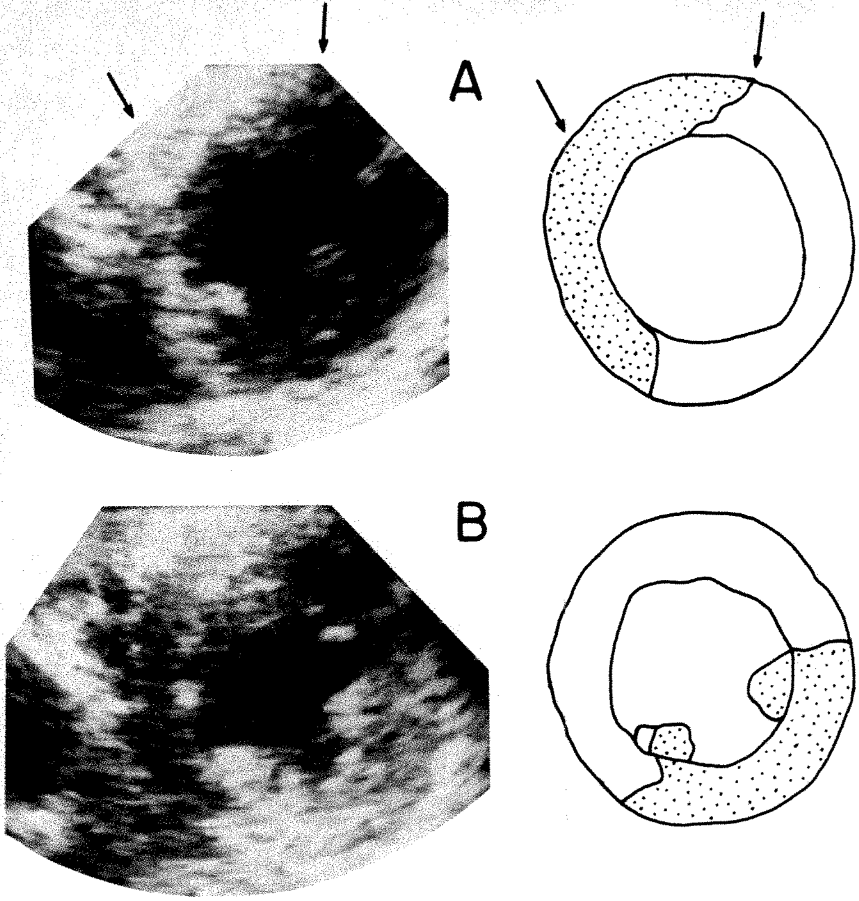


FIGURE 1. End-diastolic frames after right (*A*) and left main (*B*) injection of contrast medium in a patient with an occluded left anterior descending artery. Collateral flow is evident from the right coronary artery (indicated by arrows in A), but left main injection of contrast medium shows flow limited only to the left circumflex bed (*B*). The region not showing any contrast following both injections denotes the risk area.

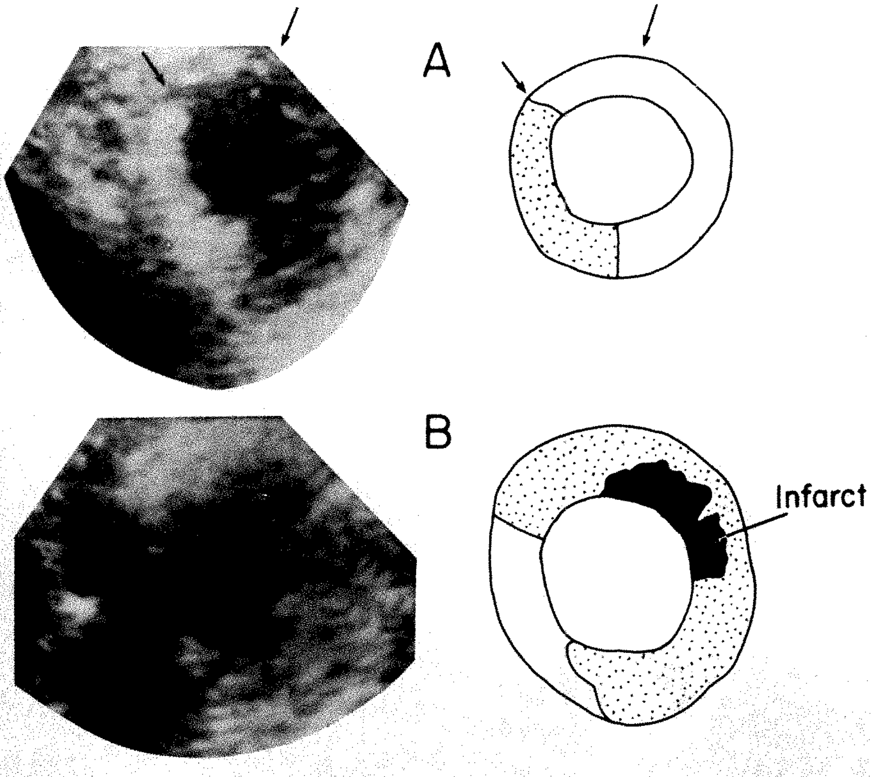


FIGURE 2. End-diastolic frames after right (*A*) and left main (*B*) injection of contrast medium following successful angioplasty of the occluded left anterior descending artery in the same patient whose images are depicted in Figure 1. After left main injection, whereas the area within the left anterior descending bed perfused previously by the right coronary artery is now well perfused, a confluent hypoperfused zone is noted within the region not supplied previously by collaterals (see Figure 1). Collateral flow is no longer evident in the left anterior descending bed from the right coronary artery (indicated by arrows in *A*).

ment in regional function 1 month postangioplasty than the former group. In addition, patients in whom angioplasty was not successful showed no improvement in regional function despite having as much collateral flow to the infarct zone as those with successful angioplasty.[32] Myocardial contrast echocardiography, therefore, has the potential of providing information regarding viability of the myocardium at the time of cardiac catheterization without recourse to nuclear imaging techniques.

Assessment of coronary blood flow reserve: Myocardial contrast echocardiography has been used successfully in patients for the assessment of coronary blood flow reserve,[33-35] and it correlates well with intracoronary Doppler flow measurements.[35] The additional advantage of myocardial contrast echocardiography is that it provides an assessment regarding the size of the perfusion bed supplied by a vessel with critical coronary stenosis.[33] Figure 4 is an example of a patient with a mid-left anterior descending artery stenosis in whom baseline left main injection of contrast shows perfusion of the entire apex in the short-axis view (middle panel). After intracoronary injection of papavarine, however, the left anterior descending bed no longer shows myocardial opacification and the left circumflex bed shows contrast enhancement (right panel). This maneuver not only demonstrates that the left anterior descending bed is critically stenosed but also depicts its perfusion bed size.

Assessment of success of coronary angioplasty: The principle behind assessment of coronary blood flow reserve can be used to assess the success of coronary angioplasty. The discrepancy in the myocardial opacification between the normal bed and that supplied by a critical coronary stenosis after intracoronary injection of papavarine should be less after successful angioplasty.[34] The degree to which this discrepancy normalizes may relate to the success of angioplasty. In addition, since coronary hyperemia may be present for several minutes following successful angioplasty, myocardial opacification may increase to the bed supplied by the vessel undergoing angioplasty.[36]

Limitations of the technique in the catheterization laboratory: The 2 common limitations for the use of myocardial contrast echocardiography in the cardiac catheterization laboratory are the logistics of having an echocardiography machine in the

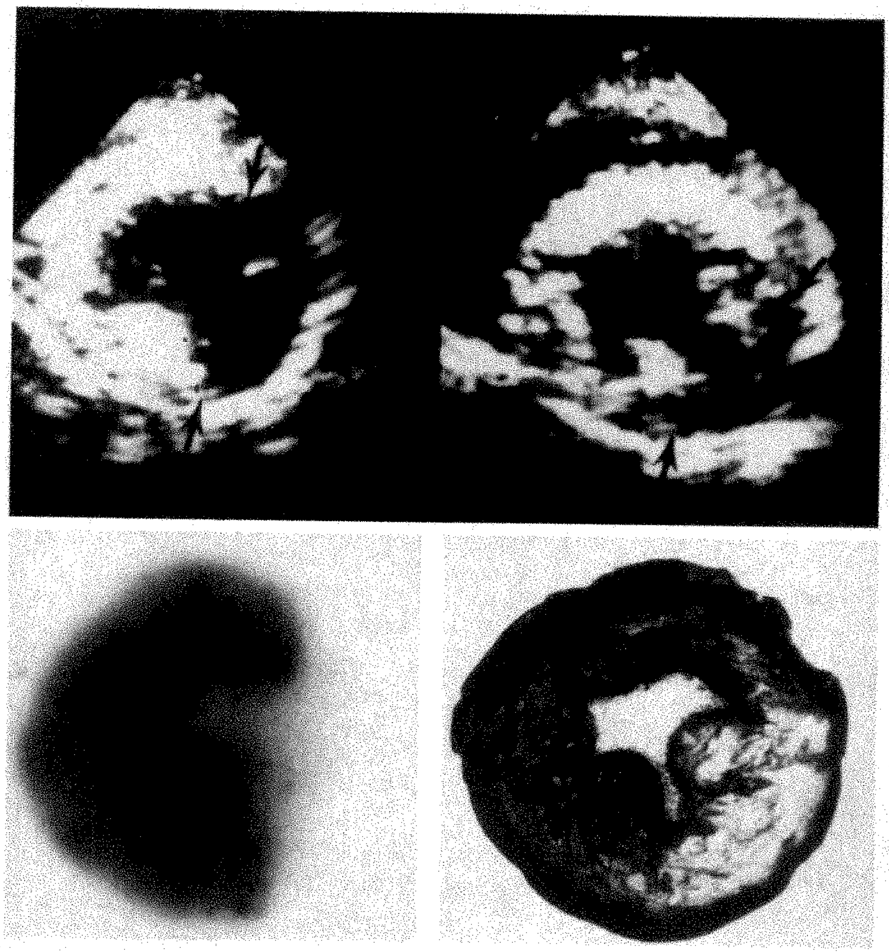


FIGURE 3. Risk area by contrast echocardiography and technetium-99m autoradiography 2 hours after occlusion (*left panels*), and infarct size by contrast echocardiography and by staining with 2,3,5-triphenyltetrazolium chloride following reperfusion. Note that the hypoperfused zone on contrast echocardiography after reperfusion, indicated by arrows in the *right upper panel*, closely predicts infarct size in the *right lower panel*. See text for details. (Reprinted with permission from American Heart Association.[24])

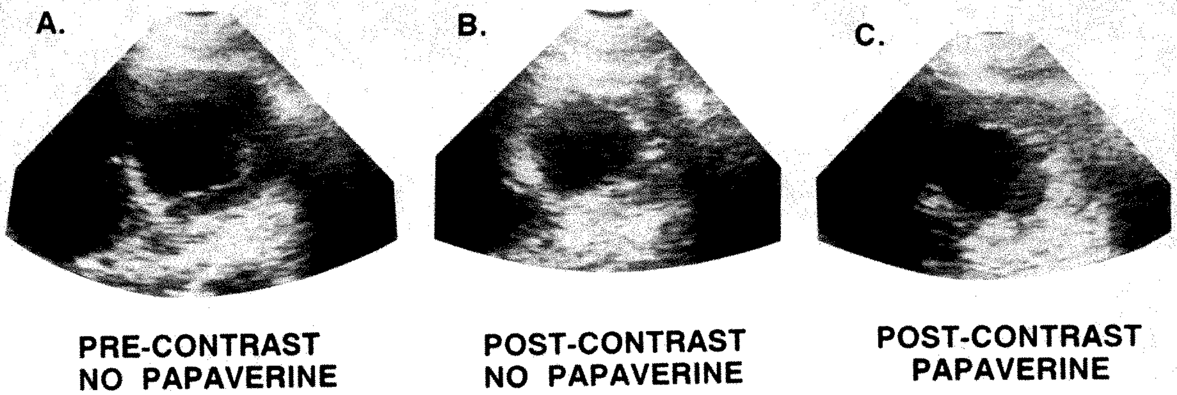


FIGURE 4. Apical short axis views in a patient in the cardiac catheterization laboratory who had a mid-left anterior descending artery stenosis. The images are obtained at baseline prior to injection of contrast (*A*); at baseline after left main injection of contrast showing even perfusion in the entire myocardium (*B*); and, after left main injection of contrast 45 seconds after intracoronary injection of 9 mg of papavarine hydrochloride (*C*). In C, the area perfused by the left anterior descending artery shows much less contrast effect than that perfused by the left circumflex artery (see text for details). (Reprinted with permission from *J Am Coll Cardiol.*[33])

catheterization laboratory and obtaining adequate images with patients lying on their backs. Both limitations are likely to be addressed in the near future by the development of dedicated echocardiographic systems with intracardiac ultrasound transducer-tipped catheters designed specifically for the cardiac catheterization laboratory. It will then be possible to place these 8–10 MHz transducers in the right heart using the femoral or internal jugular venous approach and obtain high quality images.

OPERATING ROOM

There is a significant interest in using myocardial contrast echocardiography in the operating room in patients undergoing coronary artery bypass graft surgery. Some of the applications of this technique in such patients are discussed below.

Determining route of cardioplegia delivery: When a patient undergoes bypass surgery, the aorta is generally cross-clamped and cardioplegic solution is delivered into the aortic root, from where it reaches the myocardium via epicardial coronary vessels. A patient may have such severe multivessel disease, however, that myocardial tissue may not be perfused adequately by the cardioplegic solution, leading to myocardial injury and infarction.

Myocardial contrast echocardiography can be used to assess the adequacy of cardioplegia delivery by injecting microbubbles into the cardioplegic solution and performing simultaneous echocardiography (transesophageal or epicardial). If poor myocardial opacification is noted, cardioplegia can be delivered via an alternative route. Figure 5 is a

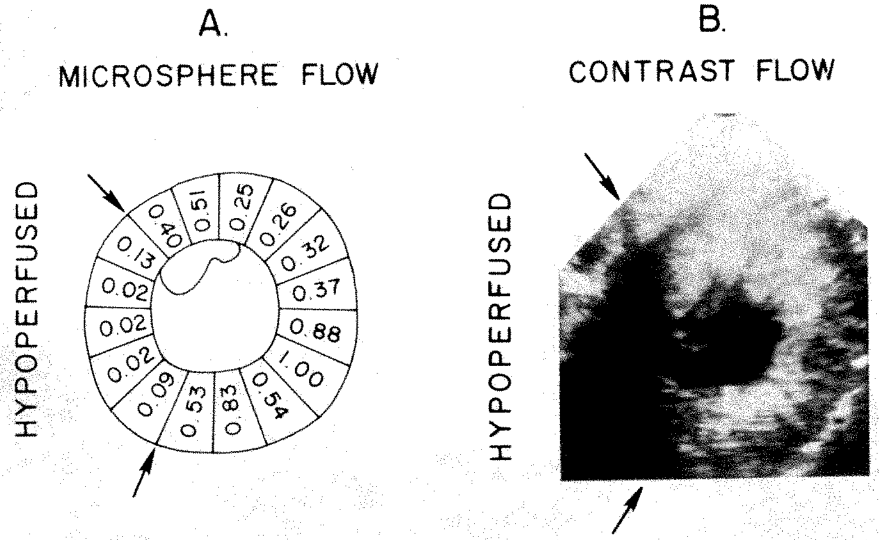


FIGURE 5. Mid-papillary muscle short-axis view of the heart in a dog in whom contrast was injected into the cardioplegia line during retrograde cardioplegia delivery via the coronary sinus. *A* demonstrates the spatial distribution of retrogradely delivered cardioplegia as measured by radiolabeled microspheres, and *B* illustrates the spatial distribution of cardioplegia flow as determined by contrast echocardiography. There is close correlation between regions receiving adequate flow by microspheres and those showing myocardial contrast enhancement. See text for details. (Reprinted with permission from *American College of Surgeons.*[37])

contrast-enhanced image acquired during retrograde cardioplegia delivery via the coronary sinus in a dog. These data illustrate that myocardial contrast echocardiography provides an accurate estimate of the spatial distribution of cardioplegia delivery as compared to radiolabeled microspheres.[38] Since there are no blockages in the venous system of the heart, cardioplegia can easily reach myocardial tissue even in patients with severe coronary artery disease. In the dog, because the coronary sinus does not drain most of the interventricular septum, the latter does not opacify when contrast is injected via the coronary sinus, as depicted in Figure 5.

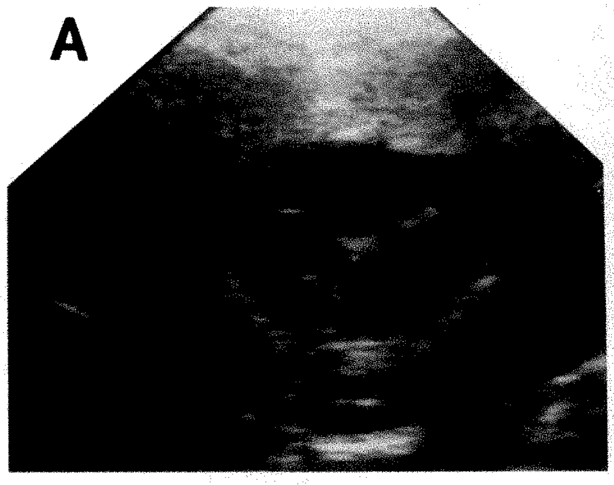
Determining the sequence of graft placement: In a patient with multivessel disease, one region of the myocardium may not receive adequate cardioplegia via the cross-clamped aorta, whereas the rest of the heart may. In such a situation, rather than completely changing the route of cardioplegia delivery from anterograde to retrograde, it may be more practical first to bypass the region not showing contrast enhancement and then to deliver cardioplegia to it via the graft before continuing with the rest of the operation.

Determining the success of bypass graft placement: Figure 6 illustrates an example of a patient with a proximal right coronary artery lesion in whom myocardial contrast echocardiography shows a lack of posterior wall opacification during initial anterograde cardioplegia delivery (panel A). After the artery has been bypassed and both distal and proximal anastamoses have been performed, repeat injection of contrast medium into the aortic root shows opacification of both the anterior and the posterior myocardium (panel B). Myocardial contrast echocardiography can, therefore, be used to determine the success of bypass graft placement in the operating room during surgery.[15,38–40] If lack of perfusion is noted and can be attributed to a technical problem, the graft can be revised. To be able to do so in the operating room may help reduce the incidence of perioperative myocardial infarction. Dedicated computer systems have been developed to determine the success of bypass graft placement on-line in the operating room.[15]

Limitations of the technique in the operating room: Unlike the cardiac catheterization laboratory, use of echocardiography in the operating room has become routine. The major limitation to the use of myocardial contrast echocardiography in the operating room is myocardial attenuation. Unlike the blood-perfused beating heart, where the microbubbles transit the microcirculation like red cells,[16] during cold, crystalloid, cardioplegia delivery, the microbubbles adhere to the endothelium of the microvessels, which is probably related to hypoxia.[41] Accumulation of microbubbles within the myocardium results in attenuation of the contralateral wall. One way to reduce this attenuation is to reduce the number of bubbles injected. Availability of commercially produced bubbles will allow a better dose titration of microbubbles in the future.

CLINICAL APPLICATIONS OF MYOCARDIAL CONTRAST ECHO IN THE YEAR 2000

All applications listed thus far require a direct intra-arterial injection of contrast medium, thereby



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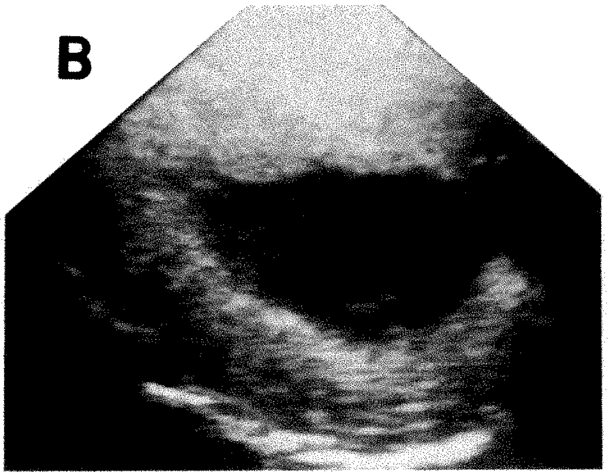

Post–CABG

FIGURE 6. Short-axis view of the heart in a patient with severe right coronary artery stenosis obtained in the operating room using epicardial imaging during bypass surgery. During aortic cross-clamping when contrast is injected into the cardioplegia solution at baseline (*A*), poor opacification is noted in the posterior wall. When the injection is repeated into the aortic root after successful placement of a bypass graft beyond the right coronary occlusion, increased opacification is noted in the same region.

limiting the widespread clinical usage of myocardial contrast echocardiography. Recently, it has been demonstrated that, when a highly concentrated solution of contrast is injected into the right atrium of dogs after intravenous infusion of dipyridamole, myocardial opacification can be achieved close to 90% of the time.[42] Normally, only 4–5% of bubbles entering the left ventricle will enter the coronary circulation. In the presence of dipyridamole, this number is significantly greater. The best results are obtained when microbubbles are used that are small enough to pass through the pulmonary circulation, but large enough to produce adequate myocardial opacification, which is in the range of 6 μm. Because the myocardial opacification produced from right heart injection is subtle, digital subtraction and color-coding techniques are required for appreciating the myocardial contrast effect.[42]

Figure 7A illustrates a short-axis image of the heart when the bubbles are in the right ventricle and have not yet reached the LV cavity. Figure 7B illustrates intense LV cavity opacification after transpulmonary passage of the bubbles with subtle myocardial opacification. The black area in the posterior aspect of the image represents attenuation produced by LV cavity opacification. Figure 7C shows an image produced by digitally subtracting the image in panel A from that in panel B. The myocardial opacification is more apparent. Several beats later, when the LV cavity opacification is less, posterior wall attenuation is also less and a subtraction image also shows posterior wall opacification. When the subtracted images are color coded, so that yellow and white implies greater opacification than orange and red, myocardial opacification is even better appreciated, as shown in Figure 8.

TABLE II Clinical Applications of Myocardial Contrast Echocardiography by the Year 2000

In the ER/CCU in patients with acute myocardial infarction
- Assessment of size of risk area
- Assessment of success of reperfusion therapy
- Assessment of extent of myocardial salvage

In the noninvasive laboratory in patients with chronic CAD
- Detection of CAD
- Risk-stratification prior to noncardiac surgery
- Risk-stratification for medical versus surgical treatment

Quantitation of myocardial blood flow

CAD = coronary artery disease; CCU = coronary care unit; ER = emergency room.

These data suggest that it may become possible in the future to opacify the myocardium from venous injection of contrast in humans. Obviously, if such is the case, applications listed in Table II will become possible. In particular, it will be possible to determine risk area during coronary occlusion prior to reperfusion.[43] If the risk area is large, then reperfusion can be attempted and the degree of myocardial salvage can be defined. Figure 9A is an example of a large risk area defined by myocardial contrast echocardiography during left atrial injection of contrast in a dog undergoing 6

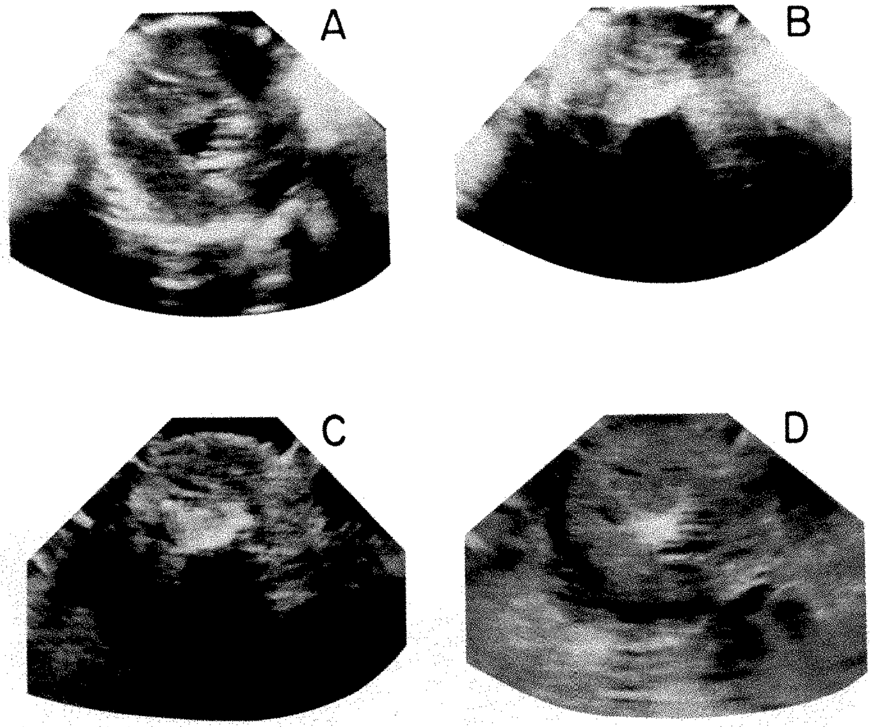

FIGURE 7. Short-axis images obtained in a dog in whom contrast has been injected into the right atrium, during its passage through the right ventricle (*A*) and after it appears in the left ventricular cavity (*B*). In *B*, intense cavity opacification results in posterior wall attenuation and subtle myocardial opacification. When the image in *A* is digitally subtracted from that in *B*, myocardial opacification is far more obvious (*C*). Some frames later, when posterior wall attenuation is diminished, a subtraction image shows opacification of the posterior myocardium as well (*D*). (Reprinted with permission from *American Heart Association*.[42])

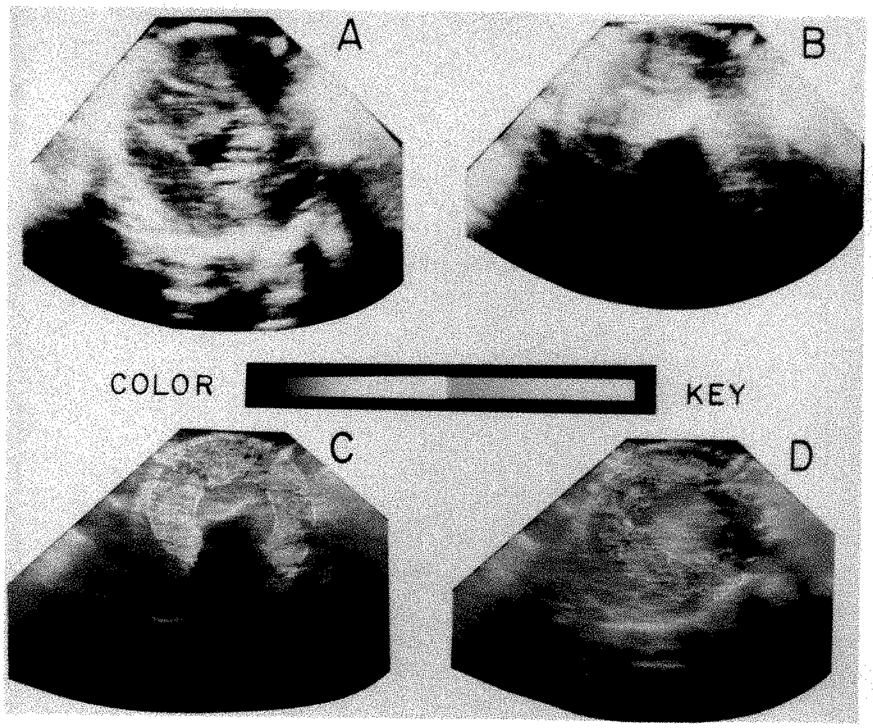

FIGURE 8. The effect of color-coding on perception of myocardial opacification after right atrial injection of contrast in the dog is illustrated. The images are the same as in Figure 7 except that the subtraction images in *C* and *D* have been color-coded using a scale where red denotes least change in pixel intensity and white, the most. Oranges and yellow are in between. (Reprinted with permission from *American Heart Association.*[42])

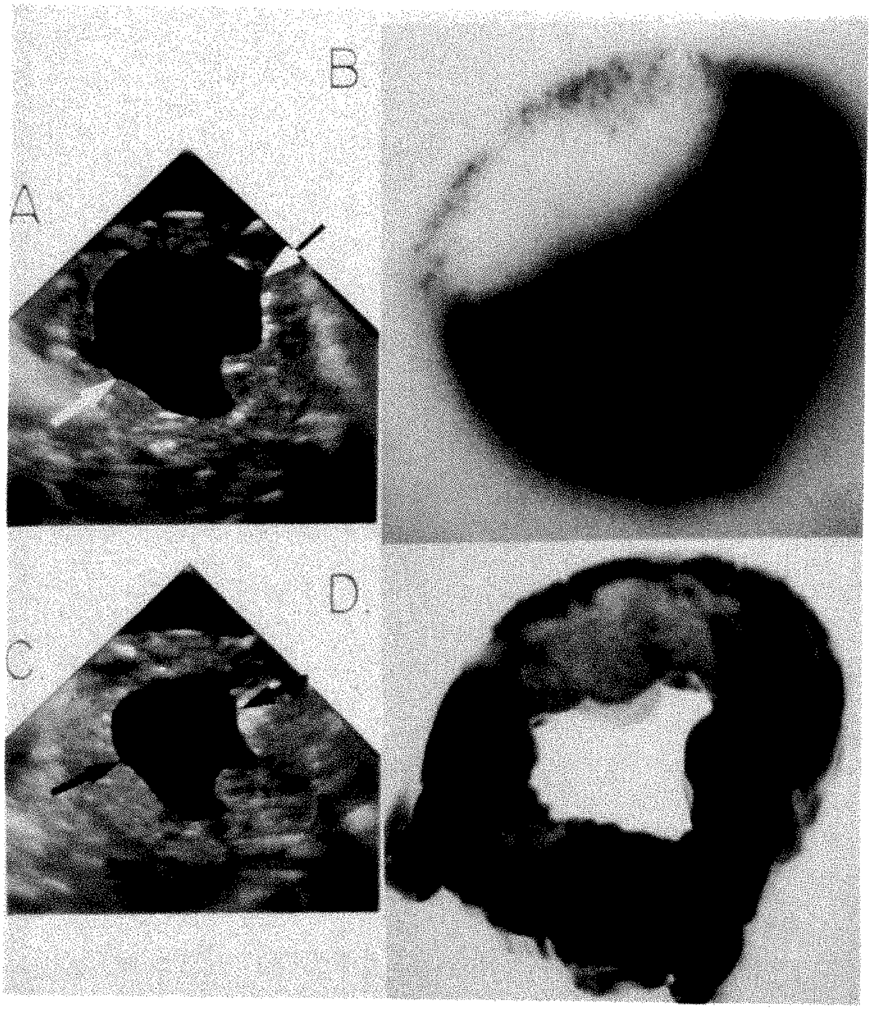

FIGURE 9. Color-coded subtraction images obtained in a dog with left anterior descending artery occlusion in whom contrast was injected into the left atrium after 6 hours of occlusion (*A*) and after 15 minutes of reperfusion (*C*). The area with hypoperfusion in *A* (denoted by arrows) corresponds to the risk area measured during coronary occlusion using technetium autoradiography (*B*). Similarly, after reperfusion, the region showing hypoperfusion in *C* (denoted by arrows) corresponds to the infarcted region on triphenyltetrazolium chloride staining (*D*). In this example, there is very little myocardial salvage despite reperfusion. See text for details.

hours of left anterior descending artery occlusion. This risk area corresponds well with that on technetium-99m autoradiography, as noted in Figure 9B. After reperfusion, myocardial salvage is minimal, as defined by a persistent defect on myocardial contrast echocardiography (panel C) which corresponds to infarct size determined by triphenyltetrazolium chloride (panel D).

Similar to dipyridamole "stress" testing with thallium-201 radionuclide imaging,[44] it will become possible to detect the presence of coronary artery disease using myocardial contrast echocardiography in conjunction with intravenous infusion of dipyridamole. Using such an approach, it will be possible to identify patients at increased risk for future events. Evaluation for noncardiac surgery plus medical versus surgical management of coronary artery disease could also be based on the results of these tests.[44] In doing so, it is conceivable that myocardial contrast echocardiography could start to replace radionuclide techniques for myocardial perfusion imaging.

Finally, it may also become possible to quantitate regional myocardial blood flow using myocardial contrast echocardiography.[45] The intravascular rheology of microbubbles have been shown to be similar to that of red cells both in the hamster cheek pouch[16] and the beating canine heart.[9] The transit rates of these microbubbles have also been demonstrated to correlate closely with regional myocardial blood flow measured with radiolabeled microspheres.[18] Quantitation of myocardial blood flow in the operating room and cardiac catheterization laboratory, as well as in the outpatient noninvasive laboratory may, therefore, finally become a reality with the use of myocardial contrast echocardiography.

CONCLUSION

Myocardial contrast echocardiography is a new technique that uses microbubbles of air in conjunction with simultaneously performed 2-dimensional echocardiographic imaging. Currently, it can be used to determine myocardial perfusion in the cardiac catheterization laboratory and the operating room. For this technique to find a broader clinical application for the assessment of myocardial perfusion, it will be necessary to opacify the myocardium following venous injection of contrast medium in humans. In this regard, enhancement in bubble engineering, optimization of echocardiographic imaging systems (greater sensitivity and dynamic range), and availability of digital image enhancement techniques will be required for myocardial contrast echocardiography to realize its full clinical potential by the year 2000.

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Discussion II: Contrast Echocardiography

Dr. Anthony DeMaria (Lexington, Kentucky): We will begin this session by discussing the importance of the contrast agent. Would the panel members agree that any potential application of contrast echocardiography is directly related to the existence of an appropriate contrast agent for clinical use? What is the current state-of-the-art in this effort?

Dr. Richard Kerber (Iowa City, Iowa): If I may refer to some data I have here in slide form, my first slide shows a transducer resting in a beaker of fluid containing the Albunex microbubble solution. In the 2 upper panels in the slide the ultrasound transducer is set at 15 decibels (dB); upper left is baseline and upper right is after 1 minute, with no visible change. The power is set at 20 dB in the 2 lower panels; baseline is on the left, and after 1 minute on the right. Here there is clearing of the contrast agent on the right, i.e., we see the dissolution of the bubbles by this higher-power ultrasound transmission.

Dr. DeMaria: What was the variable in the top panel?

Dr. Kerber: The only variable is the power setting of the ultrasound transducer. In the top panels the power setting is at 15 dB, with no visible effect on the image after 1 minute. When the power setting is at 20 dB, however, there is a very noticeable effect on the image after 1 minute.

My next slide illustrates the same phenomenon in graphic form, with time settings of 0, 1, 2, and 5 minutes. When the transmit power is set at 10, 12.5, or 15 dB, there is essentially no change over time. Again, 20 dB brings a marked change to the image.

The third slide shows that the effect also occurs when a slice of myocardium is suspended between the transducer and the fluid with the contrast agent in it. Although it is an in vitro experiment, the effect still occurs when the ultrasound waves are transmitted through a slice of myocardium. Thus, the contrast agent is sensitive to the transmit power, but this may not be true in vivo. I think we need to know the detailed characteristics of each contrast agent that is being studied. For example, Dr. Meltzer has shown that these agents are sensitive to pressure in both systole and diastole.

Dr. Gary Plotnick (Baltimore, Maryland): I would like to discuss the issue of pressure sensitivity, which is a particular problem in left ventricular (LV) cavity visualization. Perhaps in the future other agents will be developed that have different sensitivities and we will be able to utilize them to measure pressure noninvasively.

Dr. DeMaria: Dr. Meltzer has been involved in the development of contrast agents for some time. Would you give the panel an update?

Dr. Richard Meltzer (Rochester, New York): One of the most significant limiting steps in contrast echocardiography is the lack of commercially available agents. The 2 agents that are closest to being approved still require refinement. There will be a tremendous impetus to begin new research when improved agents come on the market. Improvements that are needed include pressure stability (to withstand systole and allow for carotid, transcranial, and myocardial imaging), a sufficiently small microbubble size to pass through the lungs, and the ability to survive in sufficient concentration, so it can be administered intravenously and provide hot spot/cold spot imaging for myocardial perfusion. Potential applications of contrast medium injection include edge detection, Doppler flow enhancement, and ejection fraction evaluation. There has been no in vivo work but, if it were possible to obtain both right ventricular (RV) and LV ejection fraction measurement with a single injection of contrast medium, it would have an immediate clinical application and probably be reimbursable. In short, we need to develop clinical applications in addition to contrast agents.

Dr. DeMaria: Dr. Smith, is it possible to quantitate LV function, ejection fraction, and cardiac output?

Dr. Mikel Smith (Lexington, Kentucky): We have experience with two agents that are coming to market. With Echovist we have been able to measure cardiac output by thermal dilution or indicator washout in the right heart. However, in the left heart, using either Echovist or Lebovist, the input function is so delayed and erratic that washout curves have not provided the data. One other, but less desirable, possibility is to use an agent to help better define endocardial borders and then use standard algorithms for calculating ejection fraction.

Dr. DeMaria: The standard agents do not provide quantitative precision at this time?

Dr. Benjamin Byrd III (Nashville, Tennessee): Our work on Doppler enhancement was a bit disappointing because we had hoped to see mitral enhancement, but it was just not optimal. We are also interested in effects of larger or more concentrated bubble injections, and possibly larger bubble sizes. However, until Albunex is marketed, human studies must be deferred to the future.

Dr. Alfred Parisi (Providence, Rhode Island): The goal in this field is to develop an agent, whether contrast or drug, that is standardized and universally available. Until that goal is reached, studies will produce uneven results in different areas. Albunex will get us off to the start we need in this area.

Dr. Christopher Appleton (Tucson, Arizona): For routine contrast studies of the right heart, will Albunex be more effective, predictable, and produce better images than agitated saline?

Dr. DeMaria: Dr. Smith, did you have a chance to make any observations in the right heart during your clinical studies of Albunex on border detection?

Dr. Smith: Most of the right heart indications have been replaced by conventional and color-flow Doppler. However, Albunex could very well be used to detect the significant number of atrial septal defects and patent foramen ovale missed with standard echocardiography.

Dr. Appleton: The concentrations that have been used for the left heart studies are not very useful. The right side of the heart is attenuated and nothing can be seen. Therefore, at the current dosages for transpulmonary passage, agitated saline provides much more intense opacification.

Dr. DeMaria: We have used agitated saline in our work and have opacified the right atrium in most cases.

Dr. Nelson Schiller (San Francisco, California): An important new direction would be to use contrast to enhance tricuspid jets during an intervention, particularly exercise. This is the direction of interventions with echocardiography where quantitation can be done. In the literature, Albunex has been shown to be superior to saline. The ability to administer an agent quickly and reliably, without having to agitate, and possibly even by continuous infusion, is extremely important. I believe we will be using Albunex for a long time. I also think saline is erratic, unpredictable, and discourages further physiologic testing.

Dr. DeMaria: If Albunex were available tomorrow, would you perform all of your contrast studies with it?

Dr. Schiller: Absolutely.

Dr. Parisi: In our laboratory we can obtain right heart opacification with saline, and I am sure we will also obtain it with Albunex when it comes on the market. However, when safety and effectiveness factors are similar, the decision of which agent to use most likely will depend on cost. I would anticipate that Albunex will be considerably more expensive than saline and, if so, we would probably use the special contrast agent only for certain applications where saline has been unsuccessful.

Dr. Sanjiv Kaul (Charlottesville, Virginia): It is important to realize that there is no one agent, even if the basic composition for all of them is the albumin microbubble. A different bubble concentration may be needed for different procedures. Opacifying the LV myocardium, going across the lungs, and performing intracoronary injections may all require different products or formulations. There could be 5 or 6 different formulations and the prices could vary depending on the bubble concentrations.

Dr. David Skorton (Iowa City, Iowa): The results we get from Albunex or other intravascular agents should not be directly compared with other methods that are not studying the same compartment or physiologic process. Also, the development of agents should extend far beyond better intravascular agents. Agents targeted for different procedures would expand this field in an important way. What can the experts tell us about the use of contrast for something other than intravascular transit? To what should we compare these data, given that the other ways of measuring perfusion usually are not done strictly with intravascular transit?

Dr. DeMaria: Does anyone have data on that? The fluorocarbons clearly are not utilized for their intravascular dispersion properties. They collect in areas of infarction. The disadvantage is that it takes 48 hours for them to collect, but when they do, they outline an area of necrotic myocardium.

Dr. Kaul: In terms of the question about intravascular transit, look at simple flow kinetics. Measuring myocardial blood flow requires an intravascular agent that does not diffuse or have multicompartments, but instead moves in and out of an intravascular space and has a classic function. Notice that these albumin microbubbles behave just like red blood cells in the hamster cheek pouch. When they are injected into the myocardium of a dog, their transit time relates almost 1-to-1 with that of technetium-99m-labeled red blood cells. A true intravascular agent is a very effective way to view myocardial blood flow, especially in the catheterization laboratory.

Dr. Steven Nissen (Lexington, Kentucky): Virtually all the mathematical models for looking at flow or quantitating flow assume the use of a relatively inert indicator; nothing is happening to it in the process of its transit. Various panel members have mentioned that the bubbles are pressure sensitive and accumulate in tissue. I think this proves that we need to define all the variables to get quantitative results. Is there any danger in persistent myocardial opacification? Will lighting up the myocardium for 4–6 minutes be a risk for these patients in the future?

Dr. Parisi: We did a series of experiments with much larger hydrogen peroxide particles. There was no noticeable physiologic impairment in the canine heart with the relevant doses that were used for myocardial perfusion. However, I believe that the area of reperfusion is more important in driving the field than the details of physiology. We are now intervening very aggressively with a large portion of the population with acute myocardial infarction, and echocardiography is going to play a progressively greater role in that field. If the ventricle wall is moving adequately in the acutely ill patient, the flow is adequate to sustain it. The real question is if there is no motion, but there is viability, is it possible to get the tissue to recover? That is the future of this field.

Dr. DeMaria: Very interesting. Until now, the major focus of investigation has been in enhancing border detection.

Dr. Parisi: Enhancement of border detection began about 6–7 years ago when we needed to get Food and Drug Administration (FDA) approval. Enhancement of border detection was easy to perform, and it could be done with right heart injections. That was all we needed to get FDA approval of a standard agent.

Dr. DeMaria: Are you implying that border detection is not a desirable or achievable goal?

Dr. Parisi: I think it is an achievable goal and a useful application. It also may facilitate quantification of RV or LV function. What is really important is to do the work in myocardial infarction patients who are acutely ill.

Dr. DeMaria: I think this is very controversial. Does everyone agree that border definition will play a major role in defining the endocardium of the left ventricle?

Dr. Parisi: I think it is a function of quantitation. If qualitatively you say an area is moving abnormally, you probably do not need much border enhancement. However, in performing quantification of LV function, border enhancement becomes a serious issue.

Dr. Miguel Quiñones (Houston, Texas): Absolutely. I think the answer to Dr. DeMaria's question will depend on whether the practicing community makes a major effort to try to be quantitative, because with today's equipment it would not always be necessary to use a contrast agent to make an "eyeball" assessment of a patient.

Dr. Harvey Feigenbaum (Indianapolis, Indiana): There are many factors to be considered. From a regional ventricular function point of view, the qualitative eyeball assessment seems to be not only workable, but also what most laboratories use in every technique, even in nuclear angiography. Each laboratory develops its own approaches to work out the discrepancies between qualitative and quantitative assessments. In order to quantitate, to get ejection fraction, for example, you have to have edge detection.

One of the problems with contrast echocardiography will be the cost. Because this is a new approach, we will not be able to make accurate assessments about cost until we start using it on a regular basis. Several factors need to be considered in the assessment; for example, the number of views.

Dr. Nissen: We labeled Albunex with technetium-99m several years ago and did a series of left and right heart injections in guinea pigs and rabbits. There was no trapping in any of the organs, except the reticuloendothelial system, which happened within a single pass, and it came out in the urine later. There was no evidence of recirculation.

Dr. Edward Geiser (Gainesville, Florida): Regarding the prolonged appearance of the hot spots, I would argue that this is a mechanism of hypoxia or tissue ischemia, a very low-flow state, but not trapping as I know it. It does clear and it does not get in there right away. The process is a slow uptake, long hold, slow discharge, which is similar to hypoxic states. Hearts or kidneys come back down to baseline. We have looked at intravenous Renografin injections in the heart that do not come back to baseline. Some of the iodine stays in the tissue. That hasn't happened in contrast echocardiography.

My final point relates to the significance of concentration. By hyperconcentrating the solution, you can get across the lung and into the muscle much more effectively.

Dr. DeMaria: Dr. Kaul's data relating to the collaterals are potentially very useful. These data could be employed in deciding whether to revascularize an area of myocardium that is subserving an occluded vessel. When will we have a uniform agent to test that, Dr. Kaul?

Dr. Kaul: The ones I just showed from the catheterization laboratory are sonicated Renografin, 1 ml. It takes just 40 seconds to sonicate.

Dr. DeMaria: Sonicated Renografin has a vasodilatory effect.

Dr. Kaul: Just like Renografin. That is why we measure relative flow. All the flow curve data were relative to the normal bed. Measuring actual flow requires a totally inert tracer, a substance without coronary hemodynamic or systemic effects.

Dr. DeMaria: Opacifying the cavity with contrast may form an obscuring coalescence with the border. One way to eliminate this problem is through the use of computer processing or subtraction. Will it become essential to use computer processing with contrast echocardiography in the future?

Dr. Smith: I think this approach has potential, but we have limited experience in this area. The procedure is based on the fact that precontrast or baseline images can be digitalized and subtracted from contrast-containing images, frame by frame, even in the form of a cineloop. Different algorithms are now being explored for performing the subtraction or addition, including multiplication sequences. I would like to see the next step, which would be to try to prove that what is seen is an actual border, not an artifactual border that has been created by translational motion, or through an effect of the processing.

Dr. DeMaria: Are the other panel members postprocessing these contrast images?

Dr. Smith: We are doing some, but I think there are many problems with video densitometry. Problems like trying to use video as a quantitative signal will be hard to avoid in most commercial systems, even in research systems.

Dr. Appleton: Contrast could have immediate use as an imaging technique in making decisions about reperfusion. Inject it venously, find out what is perfused, and decide which vessels to perform angioplasty in cases of multivessel disease where some of the lesions are suboptimal.

Dr. Smith: What we need in this field is digital acquisition of the echo image. Perhaps that would allow us to use smoothing, shading, or subtraction of the image to bring out differences.

Dr. Kaul: The relatively good resolution that we have always gotten has allowed us to assess qualitatively rather than quantitatively. Dr. Smith is right. The changes I see in the myocardium of my dogs with contrast echocardiography are as subtle as a thallium-201 scan in a patient. We'll have to become more sophisticated by digitally subtracting, manipulating the data, and being able to pseudocolor code the scans.

Dr. Geiser: With subtraction, if you take end diastole, keeping people with their glottis open in held expiration, looking at end diastolic beats and subtracting the serially triggered end diastoles, you can almost always get some residual subtraction in the endocardial area on a beat-by-beat basis. Once respirations are superimposed or changes occur in stroke volume, it becomes much more difficult. In addition, the mechanisms for aligning those subtractions, or making the frames registered in terms of myocardial structure, are extremely time-consuming for doing either a cross-correlation between the two frames, or some other type of feature extraction to realign them.

Dr. DeMaria: Does everyone agree that intracoronary administration of contrast will never prove feasible?

Dr. Quiñones: No, but I agree with Dr. Kaul's presentation about the collaterals and the potential for viability. We deal with these problems every day. Should we reperfuse by angioplasty or surgery an area that does not contract well? Is this muscle viable or not? These are relevant issues, and with current cross-training there are many practicing cardiologists with expertise in echocardiography. I also believe that taking the echo machine to the catheterization laboratory, if physically practical, would prove extremely beneficial.

Dr. Feigenbaum: Doing routine echocardiography in the catheterization laboratory is really not practical, and I think that at many laboratories it just would not work. What might work is to take an intravascular ultrasound at 12.5 MHz, insert the catheter in the right atrium, leave it there during an angioplasty and test it periodically. The images will be much clearer and more reproducible. Dr. Kaul's technique of using intracoronary contrast may be done in a more routine fashion, and there would be a clinically useful application for intravascular ultrasound as well as contrast.

Dr. Parisi: My comments relate to viability. Since the patient initially must have 60–70% myocardial functioning, in terms of a viability study we are really only addressing the 20–30% that is not functioning. We really need to see a contrast effect just to have an index of whether there is an intact, underlying vascular bed. To be more sophisticated and say that we also have to measure perfusion, is not a realistic current application.

Dr. Julius Gardin (Orange, California): I would advocate comparison studies with intravascular ultrasound in both pre- and postangioplasty situations to see whether it is possible to predict if an angioplasty or atherectomy would be successful. We can also use this technique to determine whether we can accomplish the same purpose by using contrast injections. If so, we can perhaps save $500–600 for a catheter if we do not have to use intravascular ultrasound.

Dr. Nissen: This technology is quite adaptable. Although it has not been implemented yet, perhaps we can have a pigtail catheter with a series of arrays separated by a few millimeters to a few centimeters that simultaneously provide a series of images. From an electronic point of view, this procedure is absolutely feasible.

Dr. Parisi: What would such a catheter cost?

Dr. Nissen: I hesitate to say, but not all these catheters are single-use catheters. If a catheter costs $1,000 and it can be used 10 times, it's very reasonable. Virtually every one of my first 50 studies were done with 5 catheters.

Dr. DeMaria: That is an important point, and I think the consensus has been that this is a long-range goal; one that does not appear to be at the threshold right at the moment.

Dr. Randolph Martin (Atlanta, Georgia): The contrast technology that we have been discussing is primarily limited to inpatient procedures. Is there going to be a role for echocardiography or perfusion testing without a catheter-based intervention? That's a critically important question if you look at the way industry is marketing positron emission tomography centers.

Dr. Feigenbaum: How complex would it be as an outpatient procedure to put a small catheter in the right brachial artery, blindly or ultrasonically place it into the root of the aorta and give an injection? It is invasive, but conceivably it could be done as an outpatient procedure.

Dr. DeMaria: As long as it goes into the aortic root and not the carotid. One last comment. We have all alluded in this session to the studies done with contrast being used to accentuate Doppler signals. What is the consensus of the panel: Will that be an important use of contrast? Will it be an ancillary role, or perhaps just used in an occasional patient?

Dr. Schiller: Occasional. We do not use it often.

Dr. Meltzer: Occasional.

Dr. Smith: A lot.

Dr. DeMaria: Is this not going to be a major indication for contrast echocardiography?

Dr. Smith: It depends on how good the agent is.

Dr. Parisi: And how important it is to know the pulmonary artery pressure.

Dr. Plotnick: Occasionally it will, I think.

Dr. Byrd: Very useful. It's just a matter of what it will cost. Exercise testing, cardiopulmonary exercise testing, is something that we will be doing much more frequently. A good contrast agent that allows us to assess pulmonary artery pressure is essential. Saline is adequate, but the newer, improved agents, if not too expensive, would be best.

Transesophageal Echocardiography: State-of-the Art and Future Directions

Bijoy K. Khandheria, MBBS, and Jaek Oh, MD

Transesophageal echocardiography complements transthoracic examination in 5–10% of patients referred to the echocardiographic laboratory. Clinical indications for performing this procedure are continually evolving. The semi-invasive nature of this procedure necessitates that it be judiciously used and that trained personnel undertake the procedure. Complications of the procedure need to be kept in mind. Future directions in the development of this technology involve newer, multiplanar, multifrequency transducers, digital archiving and retrieval, wide-field imaging, and 3-dimensional reconstruction. For the present, transthoracic echocardiography must remain the primary echocardiographic window imaging the heart, with defined clinical applications for transesophageal echocardiography.

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Transesophageal echocardiography (TEE) has rapidly become established as an integral part of echocardiographic examination, due to its superb imaging capability. The proximity of the esophagus to the heart and great vessels without many interposed structures permits high-quality imaging in nearly all patients undergoing TEE.

The concept of TEE is not new and dates back to 1976, when M-mode TEE was first reported by Frazin and colleagues.[1] The initial clinical response to TEE was tempered by the semi-invasive nature of the technique and the available technology at that time, which was a large sized transducer with no Doppler or color-flow imaging capabilities. There were <10 articles on the topic of TEE until 1980. Even with 2-dimensional imaging, the clinical utilization of TEE was limited to intraoperative monitoring of global and regional myocardial function in high-risk patients undergoing cardiac or noncardiac operations, and identification of intracavitary air embolism during upright neurosurgical procedures.[2,3] Miniaturization and the continuous improvement of TEE transducers as well as the incorporation of color-flow imaging brought this diagnostic modality to the clinical outpatient laboratory. These advances are reflected by the fact that there were >200 manuscripts dealing with clinical application of TEE in 1990.

This review deals with the current status of TEE and explores the future developments that are likely to occur with the use of TEE, from the standpoint of both technology and clinical utilization.

INSTRUMENTATION

The basic equipment for TEE is a complete 2-dimensional Doppler color-flow imaging system to which a TEE transducer can be attached. The TEE transducer is a modification of a conventional endoscope, with a small phased array or mechanical array transducer at its tip. The tip of the transducer can be controlled and maneuvered by rotary control and locking mechanism at the proxi-

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mal end of the shaft. Four distinct movements—flexion, extension, and left and right motion—are performed by the rotary control, and all of these are essential while performing a complete study. The state-of-the-art in TEE today is a biplane transducer capable of high resolution imaging, color flow, and pulse wave, as well as steerable continuous wave Doppler. The biplane transducer consists of 2 sets of 64 × 64 or 32 × 32 elements, aligned perpendicular to each other to permit imaging in 2 orthogonal planes. The shaft size of the currently available transducers ranges from 6 to 14 mm, and the tip size varies from 10 to 14 mm. The smaller size transducers provide less room for coaxial cables, and hence, there is compromise in the image quality. As of 1991 TEE transducers are capable of multifrequency imaging (3.5, 5.0, 7.5 MHz). The higher frequency, higher resolution transducers provide better anatomic delineation of structures, whereas color flow and Doppler are best performed at lower frequencies. The wide array of transducers that are available is shown in Figure 1.

Biplane transducers capable of displaying horizontal and longitudinal plane images simultaneously are also available. These transducers utilize a matrix array of crystals to perform simultaneous imaging of both planes. No clear advantage of this modality is perceived at this time except maybe to reduce the cross-talk between the 2 sets of elements. The image quality on these transducers is considerably inferior to the 64 × 64 element, non-simultaneous biplane transducers.

PATIENT PREPARATION

Prescheduled outpatient or inpatient examination is performed after the subject has abstained from oral intake of food or water for at least 4 hours prior to TEE examination. It is important to explain the procedure in great detail to the patient, and also to obtain a history of gastroesophageal-related symptoms such as dysphagia, odynophagia, or prior endoscopy. Drug allergy history is important to obtain in all instances. Dentures and oral prostheses must be removed prior to examination. Contraindications to performing TEE include esophageal pathologies such as stricture, tumors and diverticulitis, severe atlantoaxial joint disease (prohibits flexing of neck), prior radiation to the chest, and perforated viscus.

Examination is usually undertaken with the patient in the left lateral decubitus, with gentle flexing of the neck to facilitate entry into the esophagus. Although, sitting, supine, and prone patient examinations are conducted in some centers, our recommendation is to use the left lateral decubitus, to prevent the risk of aspiration. Premedication, other equipment that is required, the role of the sonographer, and training for physicians have all been dealt with in great depth in previously published literature,[4,5] as has the issue of administration of endocarditis prophylaxis.[6] The risk of bacteremia is very low and does not warrant routine antibiotic prophylaxis, except in patients with poor dentition or those with previous endocarditis, since this group is at the highest risk for developing bacterial endocarditis from transient bacteremia. A final recommendation from the American Heart Association is awaited.

ANATOMIC CORRELATIONS

Single plane TEE anatomic correlations and image orientation based along the lines of a Mayo Clinic publication[4] have gained widespread acceptance. For the horizontal plane (Figure 2), 3 primary views are obtained: 25–30 cm from the

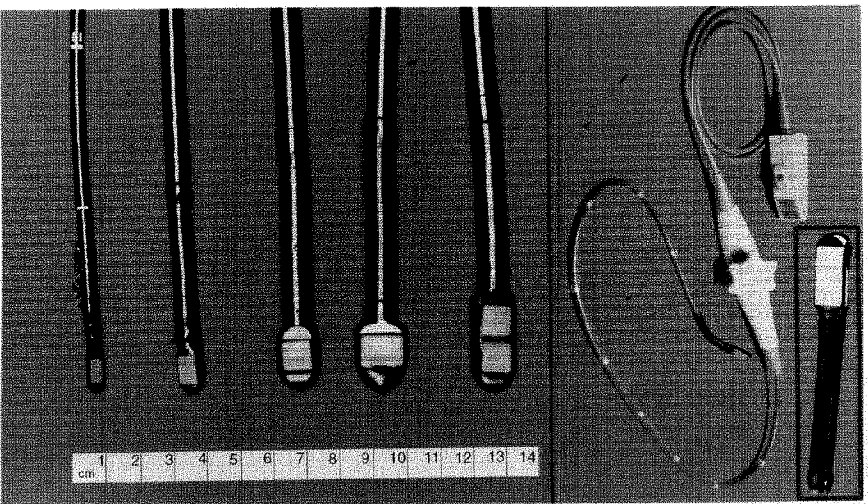


FIGURE 1. Photograph showing the different sizes of transducers that are commercially available for use in TEE. Inset shows a photograph of the 64 × 64 element biplane transducer, the current state-of-the-art in biplane TEE.

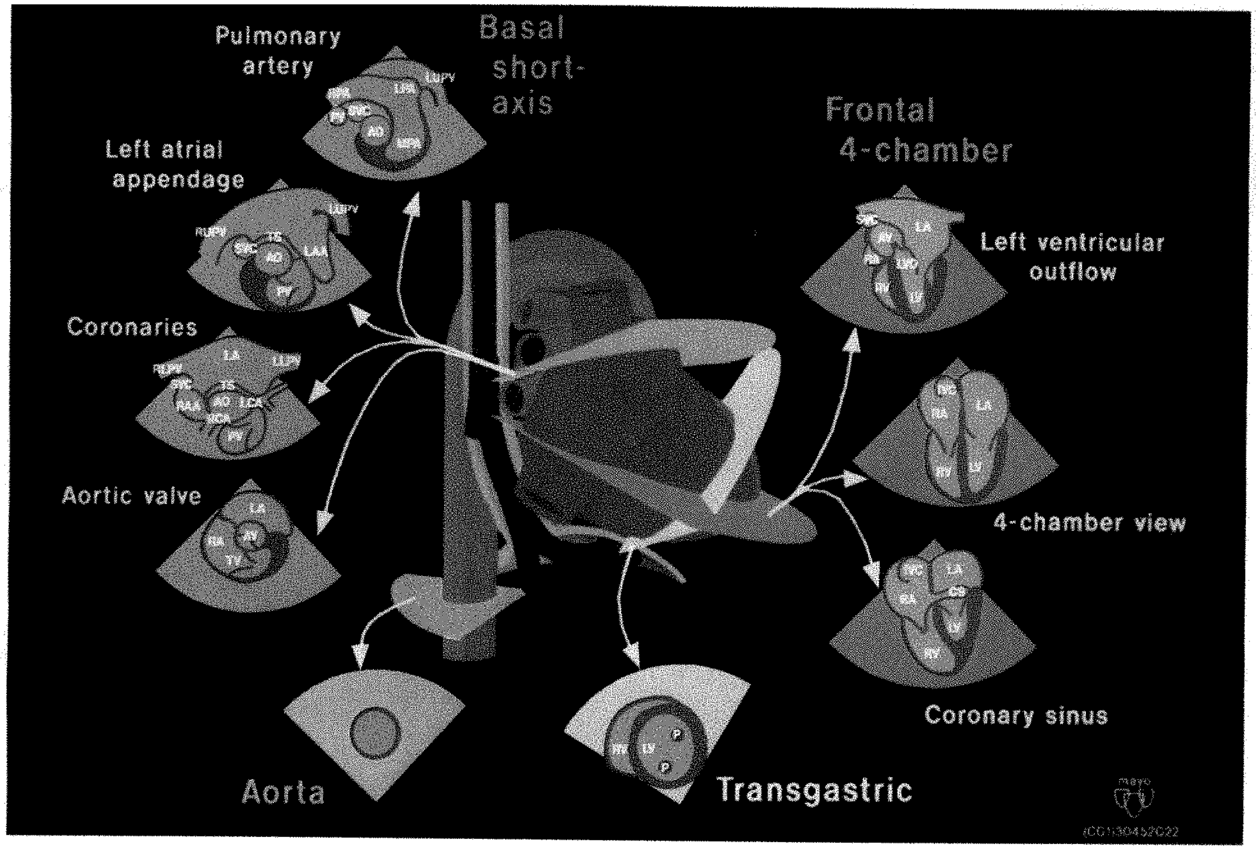


FIGURE 2. Schematic illustration depicting the various views that can be obtained in the horizontal plane. The basal, 4 chamber, and transgastric views can be obtained by utilizing up and down movement of the probe in conjunction with anteflexion and retroflexion of the transducer. Fine adjustments can be made by using the lateral flexing movement. Directing the imaging surface of the transducer posteriorly allows imaging of the thoracic aorta.

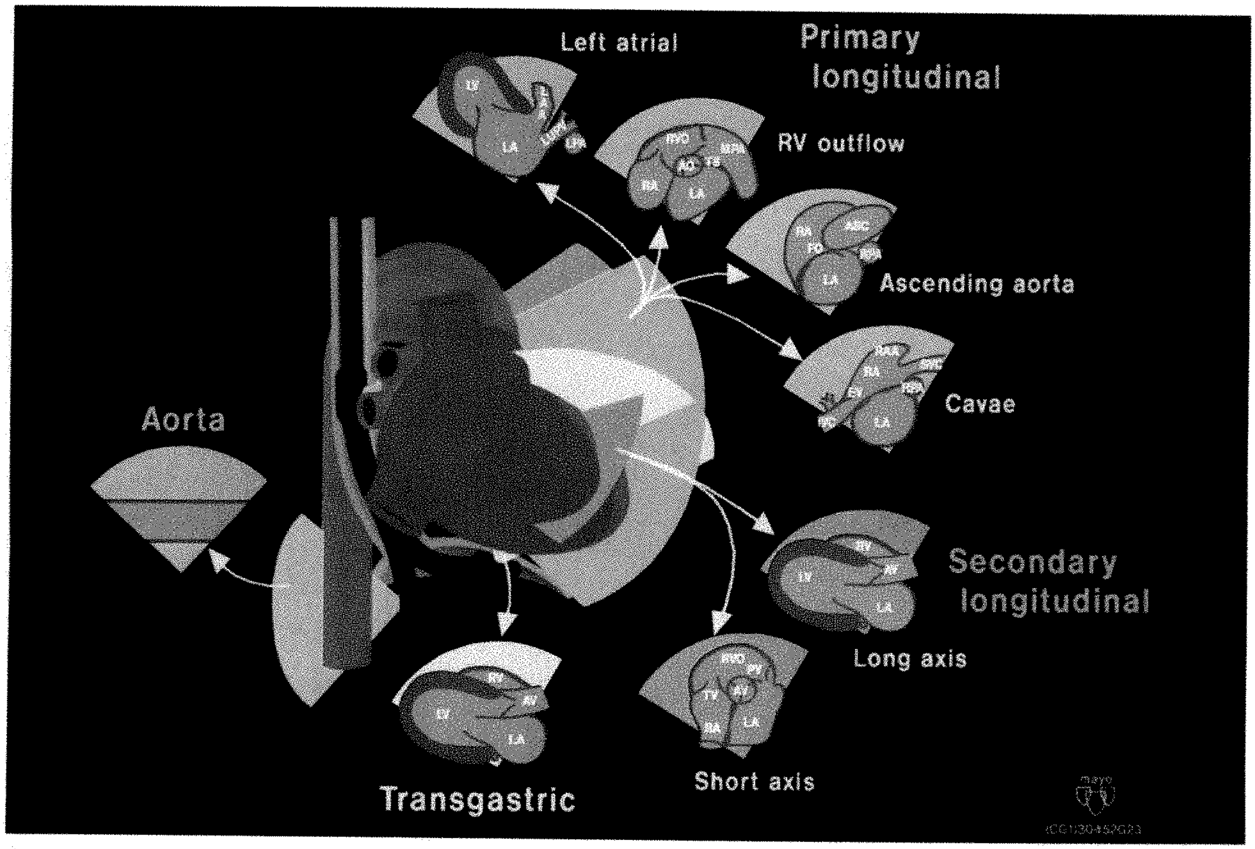


FIGURE 3. Schematic illustration depicting various views that can be obtained in the longitudinal plane imaging using a biplane transducer. Primary and secondary longitudinal views are obtained from the midesophageal position. The lateral flexing, as well as rotation of the transducer, permits visualization of all the structures in the primary and secondary longitudinal views. Transgastric views are obtained by advancing the transducer, in the fundus of the stomach, in anteflexion and side-to-side motion. Posterior rotation of the transducer enables visualization of the thoracic aorta.

incisor teeth showing the base of the heart, 30–35 cm from the incisor teeth for the 4-chamber frontal plane and 35–40 cm from the incisor teeth for the transgastric views. Longitudinal plane anatomic correlations and image orientation have also been reported by several groups of investigators.[7,8] The Mayo Clinic approach permits primary and secondary longitudinal views to be obtained from the midesophageal location of the transducer and transgastric views at 35–40 cm from the incisor teeth (Figure 3). The basis for this image orientation is to conform to an orientation that is already being used for the transthoracic approach, where the long axis views are oriented as if the observer were viewing the heart from the left of the patient; anterior structures are displayed at the top of the screen and no attention is paid to the transducer artifact (cone of the sector). This, we believe, shortens the learning curve for learning biplane anatomy, while conforming to the standards set by the American Society of Echocardiography for image orientation.[9] However, the best approach to image orientation is to utilize a format that is most familiar to the physician performing this examination and one that can be easily understood by other individuals who desire to see the images, such as other cardiology colleagues, surgeons, and anesthesiologists.

Advantages of the longitudinal orientation include obviating the "blind spot" of the aorta (proximal portion of the ascending aorta) on the horizontal plane, better delineation of the atrial septum, visualization of right ventricular outflow tract, all 4 pulmonary veins, left ventricular outflow tract, and obtaining a true cross-section of the aortic valve. Other advantages include the ability to semiquantitate regurgitant lesions better, enhance diagnostic confidence, and reduce interpretive pitfalls.

FEASIBILITY AND SAFETY OF TRANSESOPHAGEAL ECHOCARDIOGRAPHY

The multicenter European Study reported data from 15 centers on 10,419 patients dealing with feasibility and safety of this procedure.[10] The rate of unsuccessful introduction was 1.9%, the majority of which were due to lack of cooperation on the part of the patient. Complications leading to an aborted procedure were reported in 0.88% patients. There was 1 death from bleeding due to infiltration of lung cancer into the esophagus. Our own results in 3,827 procedures over 3 years are similar, with an unsuccessful intubation rate of 1.5%. Complications (major and minor) occur in 2.9% patients (Figure 4). There was 1 procedure-related death. This was an obese, middle-aged woman undergoing TEE for evaluation of mitral regurgitation. She had been premedicated with 1.0 mg of midazolam. No glycopyrrolate was used. The TEE procedure was completed successfully. However, 10 minutes following the cessation of the TEE examination, she became hypoxemic and complained of dyspnea, following which she lost consciousness. Attempts at resuscitation were unsuccessful. On autopsy, the esophagus and pulmonary arteries were found to be normal. She had evidence of lymphocytic infiltration of the myocardium consistent with myocarditis. Therefore, even though the exact cause of death could not be established, arrhythmia was suspected as being a factor leading to her death.

At the present time, it appears that 5–10% of patients undergoing transthoracic echocardiograms will undergo a TEE procedure. Our own

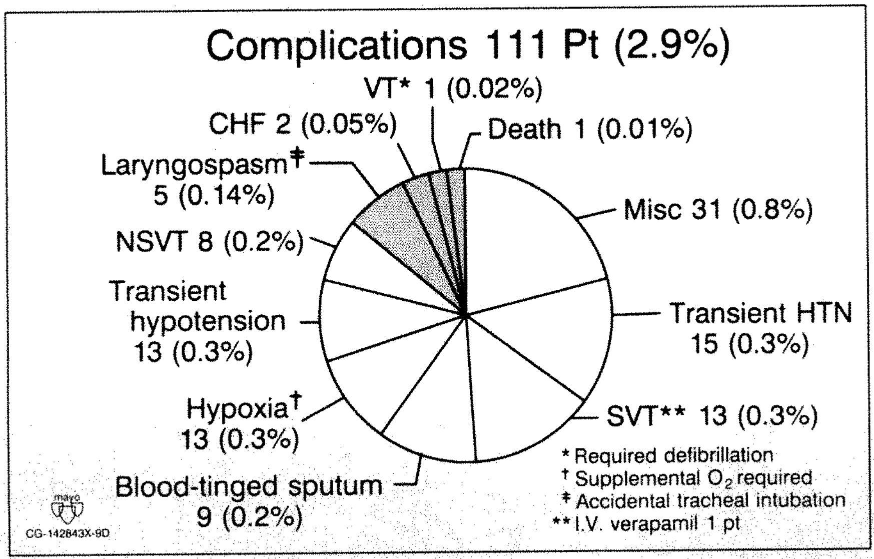
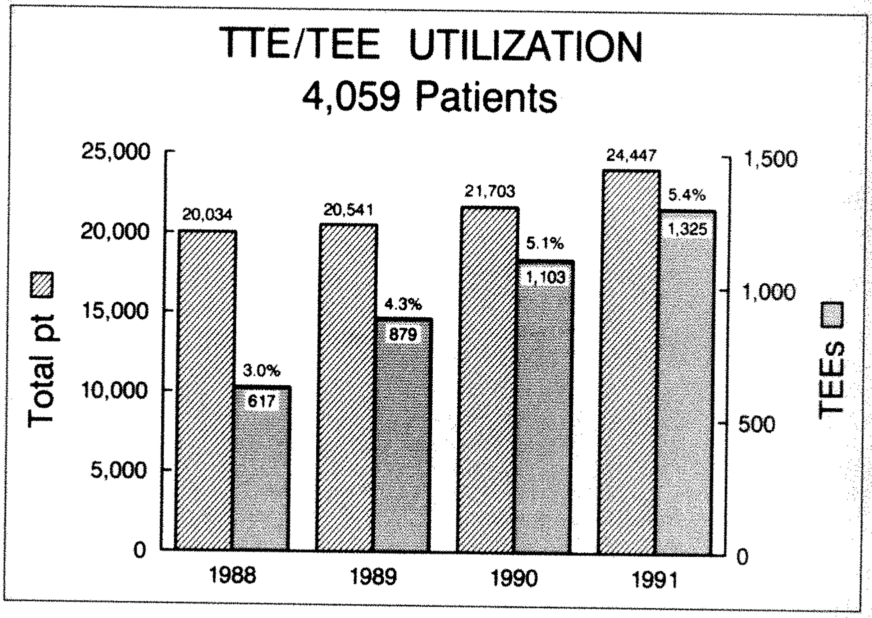


FIGURE 4. Pie diagram showing the complication of transesophageal echocardiography (TEE) in 111 patients encountered in our experience with 3,827 procedures between November 1987 and October 1991. Major complications included laryngospasm, sustained ventricular tachycardia, congestive heart failure (CHF), and death. HTN = hypertension; IV = intravenous; Misc = miscellaneous; NSVT = nonsustained ventricular tachycardia; O_2 = oxygen; pt = patient; SVT = supraventricular tachycardia; VT = ventricular tachycardia.

FIGURE 5. Figure showing the ratio of patients undergoing transthoracic and transesophageal echocardiographic (TTE and TEE) studies between 1988 and 1991. Note that increase in the number of patients undergoing echocardiograms over the 3-year period with corresponding increase in absolute numbers of patients undergoing TEE.



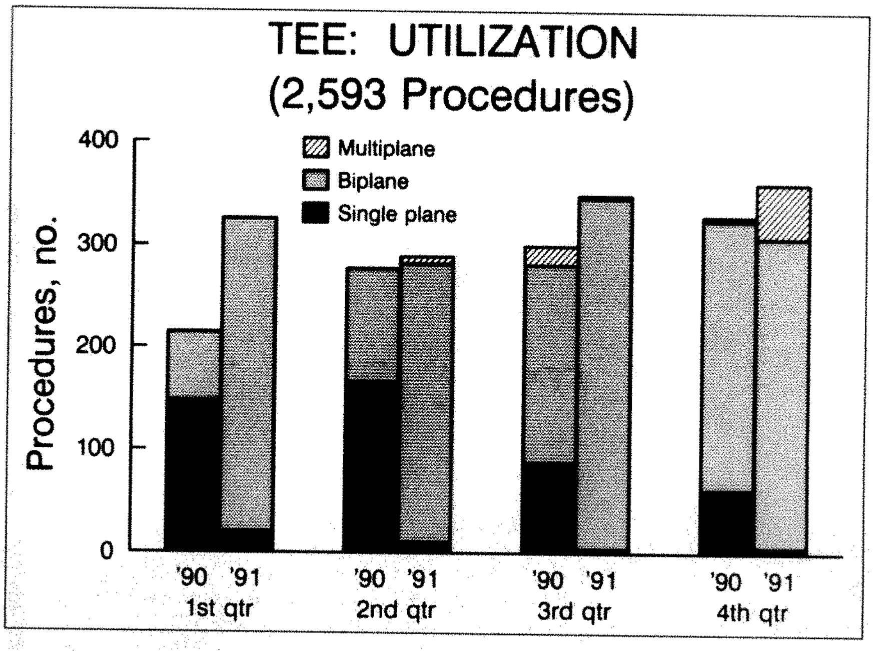
experience shows that 5–7% of patients undergoing transthoracic echocardiograms will require a TEE examination (Figure 5). At our institution, biplane TEE is making single-plane technology obsolete, as shown by our experience for 1990–1991 (Figure 6).

Indications for TEE at our institution in 3,827 patients over 3 years (Figure 7) appear to parallel reports from the other centers, including the European Multicenter data bank. Center to center variations are likely to occur, due to referral bias or excellence of certain centers in dealing with specific pathologic lesions. By and large, the indications for performing TEE encompass the list of pathologic conditions encountered at primary, secondary, or tertiary care facilities, although the frequency of disease may be different. Clearly, almost every pathologic condition in cardiology, in a selected subgroup of patients, may warrant TEE examination.

APPLICATIONS

Source of embolism: Echocardiography has long been used to evaluate patients with a suspected embolic event, presumably from the heart. The yield of transthoracic echocardiography (TTE) has been limited due to reasons such as suboptimal images in patients with chest deformities, chronic obstructive lung disease, obese individuals, the inability to visualize the left atrial appendage in a large majority of adult patients, inadequate or incomplete visualization of the left atrium and left

FIGURE 6. Bar graph showing the proportion of single-plane versus biplane transesophageal echocardiography (TEE) examinations at our institution between January 1990 and December 1991 in 2,214 patients.



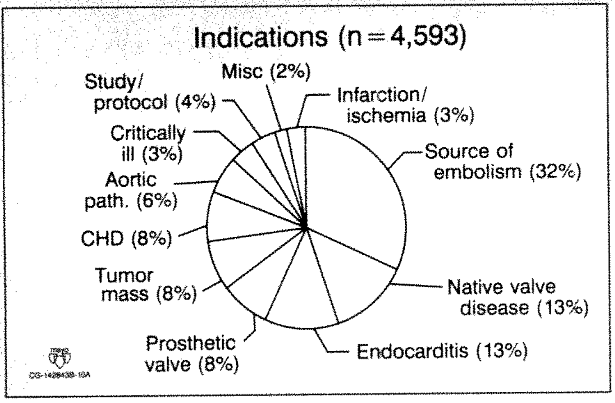


FIGURE 7. Pie diagram showing the referral diagnosis for 3,827 patients. Note the difference in the number of patients and indications, reflecting the fact that 1 patient may have undergone TEE procedure for more than 1 indication. CHD = congestive heart disease; Misc = miscellaneous; path. = pathology.

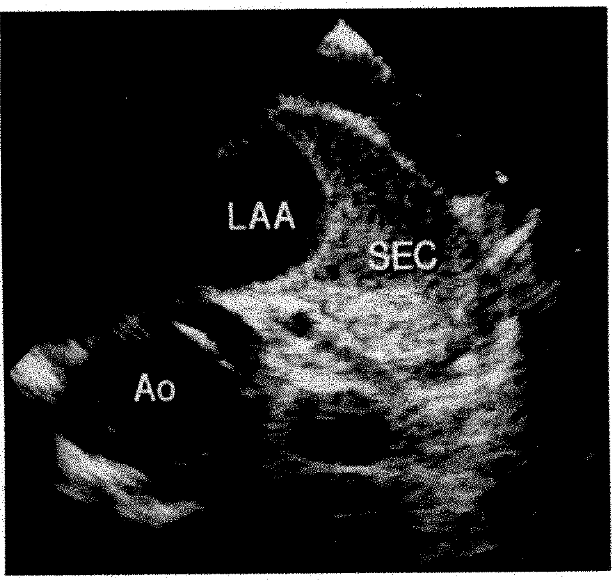


FIGURE 8. Still frame from a patient with dilated cardiomyopathy who had an embolic event. Horizontal plane image at the base of the heart showing dense spontaneous echo contrast (SEC) in the left atrial appendage (LAA). The aorta (Ao) is seen posterior to the left atrium and appendage.

atrial appendage in patients with prosthetic material (due to masking and attenuation of ultrasound beam by the prosthetic material), and oftentimes inadequate visualization of the atrial septum for making the diagnosis of patent foramen ovale. TEE has been found to have a significantly higher yield in diagnosing and detecting a potential cardiac source of cardioembolism.[11–13] These studies assume that abnormalities such as mitral valve prolapse, spontaneous echo contrast (Figure 8), patent foramen ovale (Figure 9), intra-aortic debris, or atrial septal aneurysm (Figure 10) are all a direct cause of the embolic event in the given patient population under investigation. Therefore, one must observe caution in the interpretation of these studies, since not all of the entities described can be clearly ascribed to be the cause of unexplained embolic events. Abnormalities such as atrial septal aneurysm, patent foramen ovale, mitral valve prolapse, or spontaneous echo contrast merit further studies prior to being implicated as the definite source of cardioembolic events.

Intra-aortic debris has generated considerable interest in the literature and can also represent the potential source of an embolic event, especially if one finds the embolism to be a downstream phenomenon.[14] It has been shown to be an independent risk factor for systemic embolization in a case-control study with odds ratio of 3.2; 95% confidence interval (CI), 1.6–6.6; $p < 0.001$.[15] It is clear that this diagnosis is best made using TEE, and no other imaging modality can define the abnormality better than TEE.

Native and prosthetic valvular heart disease: The role of TEE in evaluation of native valvular heart disease merits some discussion. TEE has been used to planimeter the aortic valve area,[16] with correlations that are excellent when compared with transthoracic Doppler study or cardiac cathe-

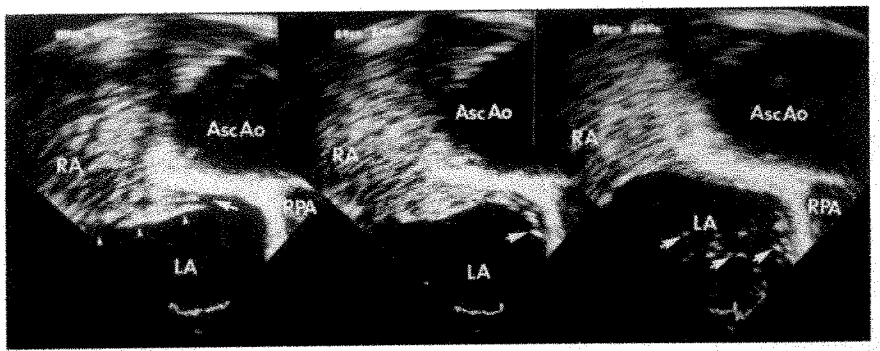


FIGURE 9. Composite of still frames from a young patient undergoing TEE for evaluation of an embolic event. Longitudinal view at midesophageal level, showing the left atrium (LA), right atrium (RA), ascending aorta (Asc Ao) with a patent foramen ovale (arrow), and floppy valve of the fossa ovalis (arrowheads). Contrast injection using indocyanine green and saline reveals a right to left shunt as demonstrated in the sequence of images in this composite figure. Right pulmonary artery (RPA) is also seen on the extreme left image.

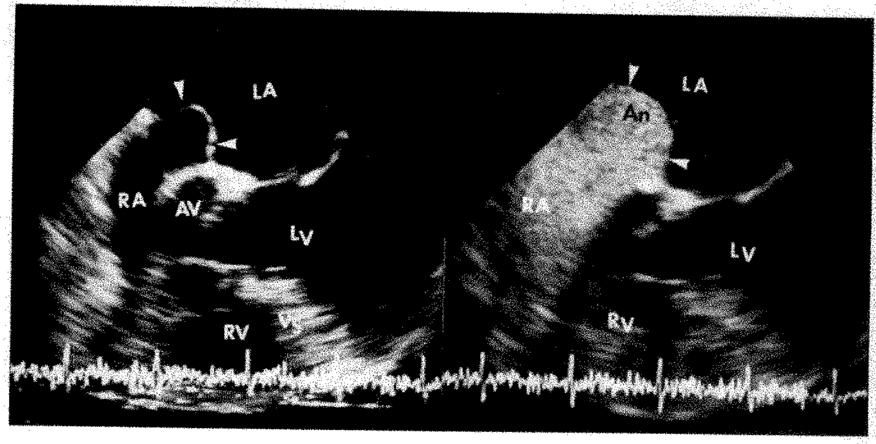


FIGURE 10. Composite of still frames, 4-chamber view in the horizontal plane showing the bulging of the atrial septum (arrowheads) in the region of the fossa ovalis. This is an example of atrial septal aneurysm. Contrast injection in this particular patient did not reveal a right to left shunt, but helped delineate the atrial septal aneurysm (An, arrowheads) as shown on the *right panel*. LA = left atrium; RA = right atrium; LV = left ventricle; RV = right ventricle; VS = ventricular septum.

terization. The availability of high frequency transducers results in better anatomic definition of the valve, and TEE may have some merit in determination of the aortic valve area, especially in patients who have suboptimal examination from the transthoracic approach. Continuous wave Doppler with TEE has not yet been established to be of significant value when dealing with the aortic valve and hemodynamics of the aortic valve.

TEE appears to provide a higher prevalence in detection of mitral regurgitation (MR), although this is a source of debate in the literature. Semiquantitation of MR remains elusive by TEE. Biplane TEE appears to be a better method for semiquantitation of MR than either of the 2 planes taken individually.[17] Utilizing the maximum regurgitant jet area from 2 planes provides the best correlation for estimating the severity of MR. Reversal of pulmonary venous systolic flow, blunting of the systolic component of pulmonary venous forward flow, or higher antegrade velocities across the mitral valve are some of the other factors that are utilized when making a comprehensive assessment of the severity of MR by TEE.[18] Structural abnormalities of the mitral valve are better assessed by TEE,[19] and as a result TEE has been shown to be a useful adjunct in evaluation of patients undergoing mitral balloon valvuloplasty. In addition to providing improved visualization of the mitral valve and its supporting structures, TEE permits visualization of the left atrium and left atrial appendage for the presence or absence of thrombus, making the procedure somewhat safer. Continuous wave Doppler with TEE allows calculation of the hemodynamics across the stenotic mitral valve (Figure 11) and also enables one to

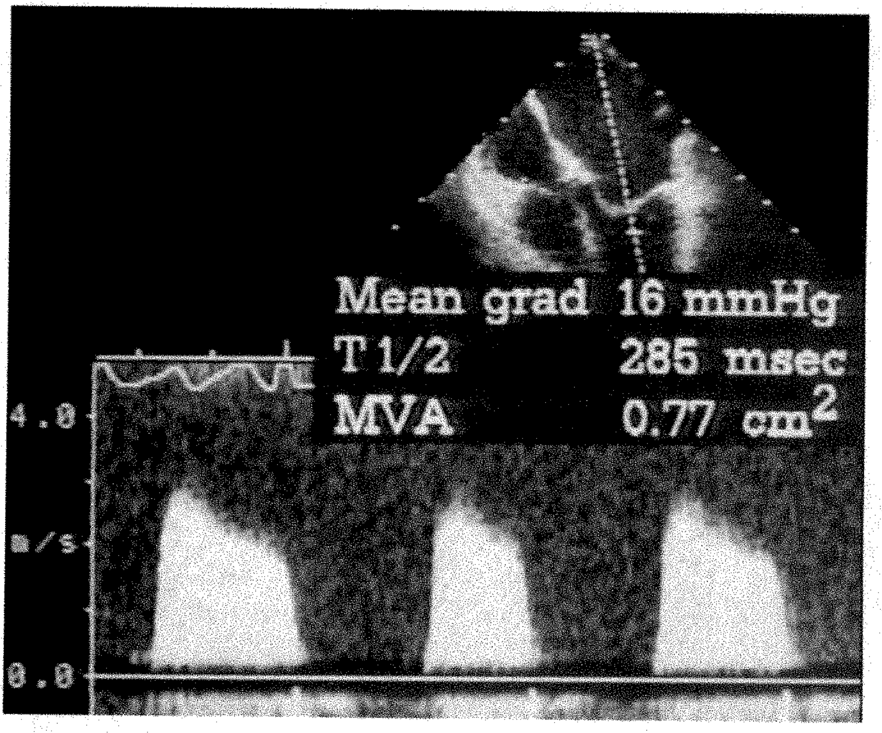


FIGURE 11. Still frame from 62-year-old woman undergoing transesophageal echocardiography (TEE) prior to mitral balloon valvuloplasty. Continuous wave Doppler interrogation of the valve reveals severe mitral stenosis (mitral valve area [MVA] = 0.77 cm^2) with a corresponding elevated mean gradient (grad; 16 mm Hg).

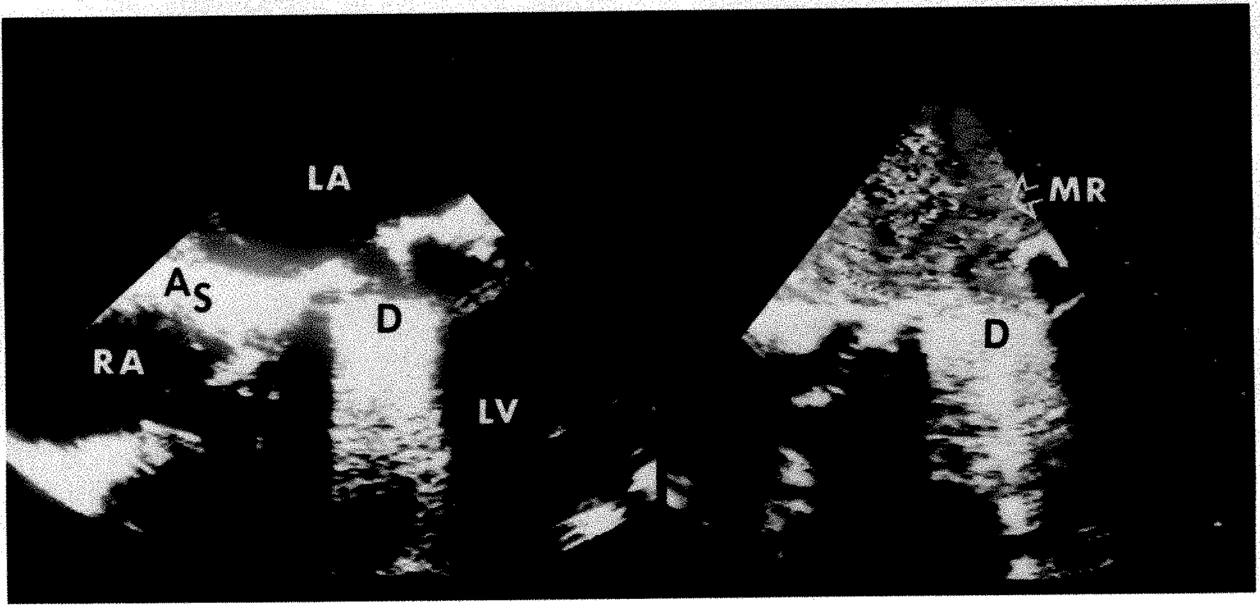


FIGURE 12. Composite of still frames (2-dimensional transesophageal echocardiography (TEE) and color flow imaging) in a 56-year-old patient with disk prosthesis in the mitral position and a new murmur, hemolytic anemia. Four-chamber view in horizontal plane showing the prosthesis (D), left atrium (LA) which is enlarged, left ventricle (LV), atrial septum (AS) and right atrium (RA). Color flow imaging (*right panel*) exhibits a mosaic of blue and red jet filling the entire left atrium, clearly indicative of severe mitral prosthetic regurgitation (MR).

obtain the pulmonary artery pressure for grading the severity of pulmonary hypertension.

TEE has been shown to overcome the problems associated with attenuation and masking that is commonly encountered when evaluating prosthetic mitral valves from the transthoracic approach. The sensitivity of TEE in detecting mitral prosthetic-related abnormalities is high, and this clearly is the technology of choice when mitral valve prosthetic abnormalities such as perivalvular regurgitation (Figure 12), endocarditis and its complications, embolic events in conjunction with a prosthesis, cusp abnormalities in tissue prostheses, and malfunction of valve repair and ring implantation are to be diagnosed.[20] This does not mean that all patients with prosthetic valves should be subjected to a TEE procedure. One must utilize a combina-

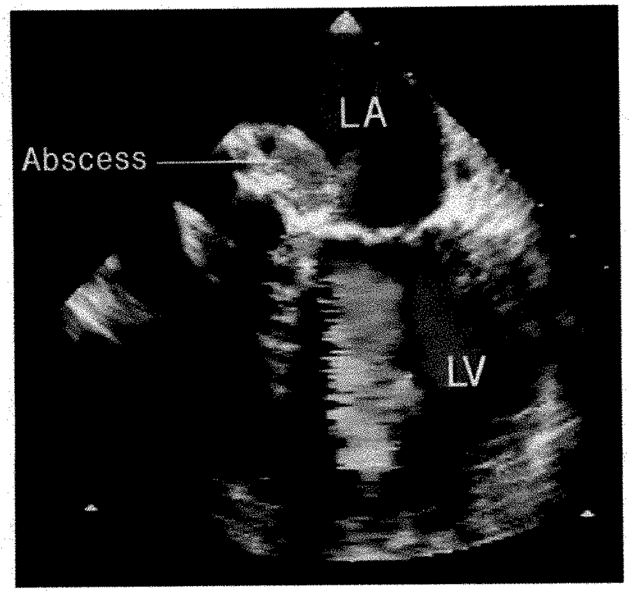


FIGURE 13. Still-frame image in the horizontal plane from a middle-aged man with staphylococcal bacteremia, heart block and murmur of indeterminate etiology. A large abscess cavity around the aortic root is shown. Communication between the left ventricular outflow tract and the cavity is seen by the presence of color in the cavity. LA = left atrium (LA); LV = left ventricle (LV).

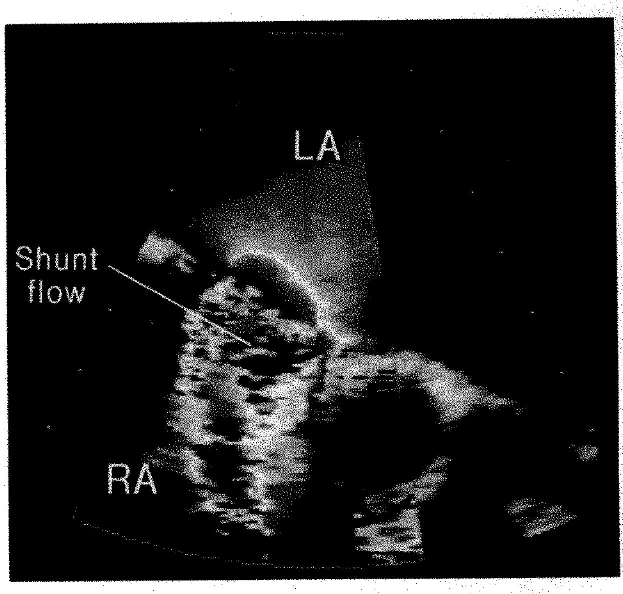


FIGURE 21. Color-flow imaging in a patient with secundum atrial septal defect. Shunt flow is clearly visualized as a mosaic of colors, indicating turbulent flow through the defect. LA = left atrium; RA = right atrium.

tion of clinical clues and TTE Doppler data abnormalities prior to making the decision for undertaking TEE. Elevated antegrade velocities, elevated mean gradients, reversal of flow in the pulmonary veins, strong signal on continuous wave Doppler of MR, and inadequate images from transthoracic imaging are some of the findings that should be clues for the recommendation of TEE.

One needs to keep in mind the fact that all mechanical prostheses have inherent regurgitation commonly referred to as "closing volume." This would be considered as "normal" regurgitation and must not be mistaken for abnormal, pathologic regurgitation requiring intervention. Recent publications have attempted to define criteria for normal versus abnormal regurgitation.[21–23] The role of TEE continuous wave Doppler in patients with prosthetic valves needs to be defined, but the obvious benefits only seem to be additive to the standard TEE examination.

Data for aortic valve prostheses are lacking, and although diagnostic accuracy for detection of endocarditis-related complications of aortic prosthesis is high, other aortic prosthetic malfunctions need further evaluation.

Bacterial endocarditis: The advent of echocardiography has made a major impact on the recognition and management of patients with suspected endocarditis. It is also clear that as the resolution of ultrasound machines has improved, the diagnostic yield of echocardiography has increased (Figures 13 and 14). TEE is highly sensitive and specific for the diagnosis of vegetations, and when the TEE study is negative, the probability of disease is low.[24] The diagnosis of abscesses associated with endocarditis is made early and in a superior fashion by TEE, as shown in a recently published study dealing with 118 consecutive patients.[25] Complications of endocarditis such as abscess formation, once recognized in a timely fashion, can alter management leading to early surgery, if progression is noted by TEE.[26]

Noninfective masses: TEE has been found to be superior to TTE for characterization and localization of noninfective masses.[27] TEE provided new or important clinical information beyond that derived from TTE in patients with left atrial or left atrial appendage thrombi, right atrial masses, and extracardiac lesions and was assessed as having influenced the management of patients most in these areas (Figures 15 and 16).

Aortic pathology: The role of TEE in diagnosis of aortic dissection (Figure 17) is well established. TEE has been found to be as good or even superior to comparable imaging technology, such as aortography, contrast enhanced computed tomography, and magnetic resonance imaging.[28,29] TEE is also useful in detection of other pathology of the aorta, such as intra-aortic debris (Figure 18) and aortic ulcer. Blunt chest trauma can result in traumatic rupture of the aorta, the diagnosis of which can be made by TEE.[30] It is clear that TEE is emerging as

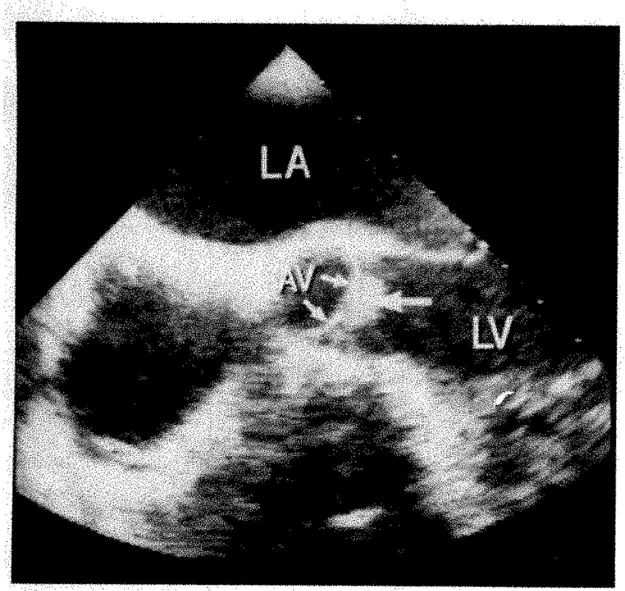


FIGURE 14. Aortic valve (AV) endocarditis with vegetation (*arrow*) in a patient with clinical evidence of subacute bacterial endocarditis. The horizontal plane still frame clearly delineates this infection. LA = left atrium; LV = left ventricle.

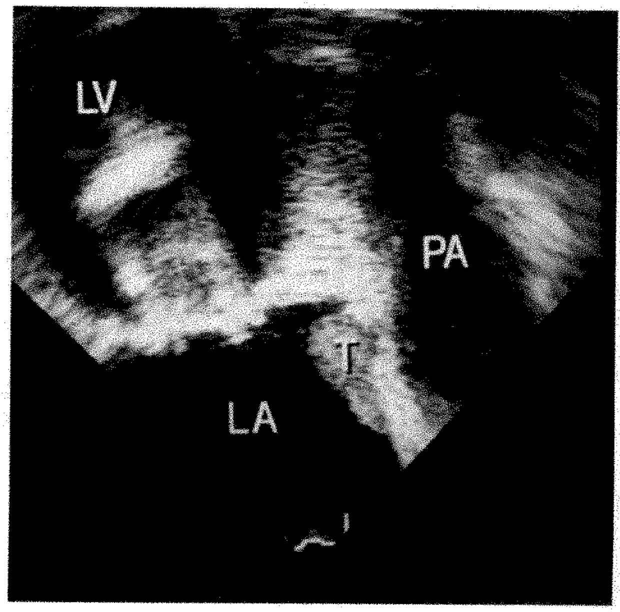


FIGURE 15. Still frame from the longitudinal plane, 2-chamber view showing the presence of a left atrial thrombus (T), which could not be identified on transthoracic echocardiogram. This patient has a mechanical prosthesis in the mitral position that is causing shadowing into the left ventricle. LA = left atrium; LV = left ventricle; PA = pulmonary artery.

the technology of choice when it comes to screening patients with suspected disease of the aorta. Biplane TEE has obviated the "blind spot," a part of the arch that was incompletely seen on single-plane TEE. One can easily identify the true and false lumen, entry site, and extent of dissection using TEE. The information is available rather quickly and can aid the surgeon in the decision to operate promptly, resulting in improved patient care and possibly decreased mortality.

Critically ill patients: TEE has had an enormous impact on the management of patients who are critically ill and need prompt, accurate diagnosis. It is feasible as well as safe to perform TEE studies in patients who are critically ill, as demonstrated by studies in the literature.[31,32] If anything needs to be stated, it is that this technology is being underutilized in the critically ill patient. The clinical impact of a negative TEE study is equally as important as a positive study.

Assessment of complications of myocardial infarction (Figure 19), hypotensive patients, patients with persistent hypoxemia suspected of having a right to left shunt (Figure 20), patients in shock, or brain dead individuals being considered as donors, are just some of the examples of how this technology is useful in the intensive, critical care units.

Congenital heart disease: The role of TEE is limited in evaluation of neonates, infants, and children with congenital heart disease, whereas TTE provides almost all the needed data in these patients. TEE in the operating room has become very useful in this group of patients. In addition to this, the use of TEE in children undergoing interventional cardiac catheterization has been described to be of use as a guiding and monitoring tool.[33] TEE was utilized for monitoring or guiding procedures such as aortic valve or pulmonic valve dilation and Mustard baffles. TEE could be performed without any complications. Adults with congenital heart disease are more suited for TEE.[34,35] TEE is also being utilized for better visualization of shunt flow across atrial septal defects (Figure 21), guiding of a clamshell device to close atrial septal defects, diagnosis of cor triatriatum, and other abnormalities.

Intraoperative transesophageal echocardiography: The role of intraoperative TEE has been well defined in mitral valve repair procedure.[36,37] It is also useful in patients undergoing surgery for hypertrophic cardiomyopathy. Intraoperative TEE has been found to be valuable in children with congenital heart disease.[38] TEE is clearly making major inroads in the management of patients in the operating room and has been found to demonstrate abnormalities that could not be shown preoperatively, thereby facilitating the surgeon in planning for the unexpected abnormalities.[39]

The role of TEE for the monitoring of ischemia remains controversial and should be utilized by trained individuals.[40,41] There is potential for utilizing this technique in high-risk patients undergoing noncardiac surgical procedures, but more data are required prior to making this a routine technique.

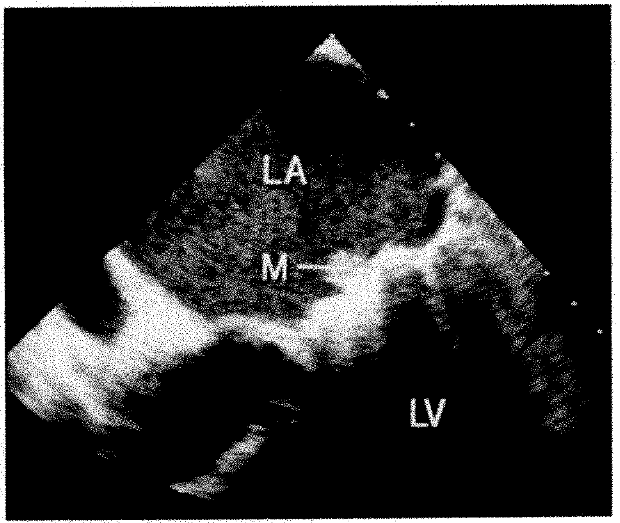


FIGURE 16. Horizontal plane 4-chamber view from a patient with mitral valve prosthesis showing the presence of spontaneous echo contrast in an enlarged left atrium (LA), thrombus on the prosthesis (M), LV = left ventricle.

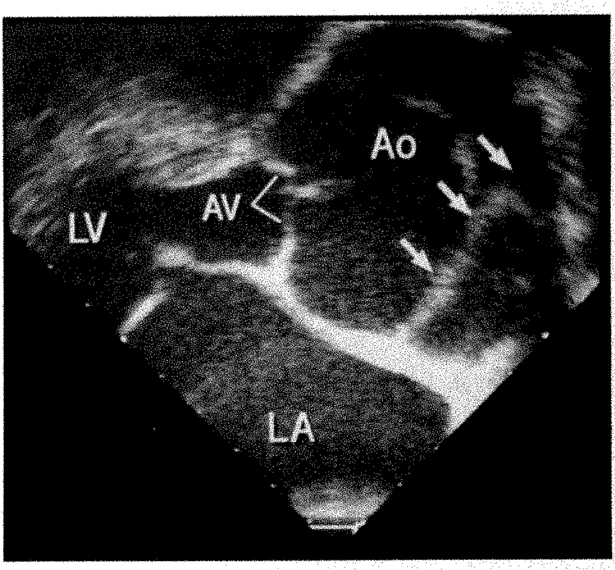
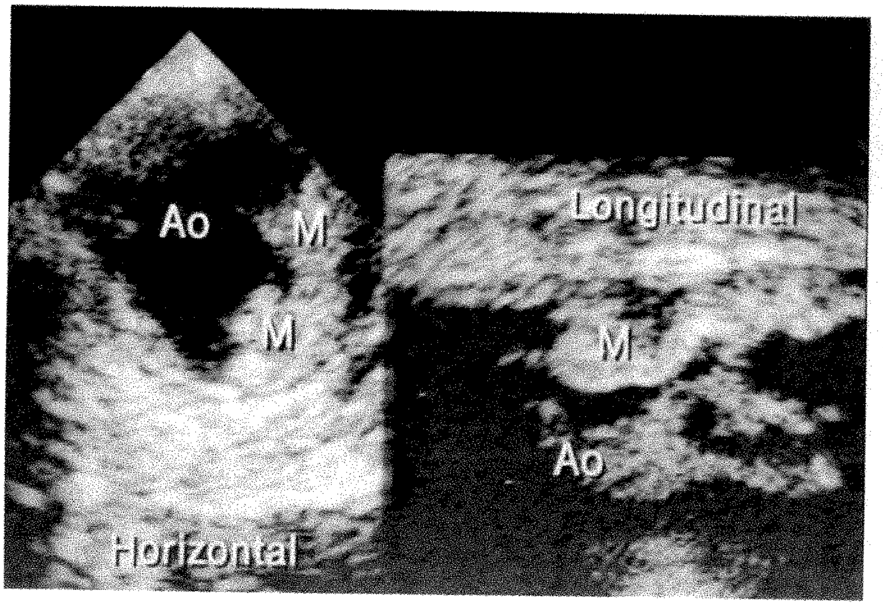


FIGURE 17. Longitudinal plane view showing the proximal portion of the ascending aorta (Ao) in a patient with aortic dissection. Intimal flap is clearly visualized (*arrows*) in the dilated aorta. This patient had type A dissection and underwent operation on the basis of transesophageal echocardiographic (TEE) findings. LA = left atrium; AV = aortic valve leaflets; LV = left ventricle.

FIGURE 18. Complex intra-aortic debris in a patient undergoing transesophageal echocardiography (TEE) for evaluation of peripheral arterial embolism. Composite of the horizontal plane image (*left*) showing the descending thoracic aorta (Ao) with the debris (M) and the longitudinal plane (*right*) showing the debris.



FUTURE DIRECTIONS

Technology: Echocardiography is a tomographic technique, and hence it stands to reason that the more numbers of tomographic planes that are available, the more precise is the diagnostic accuracy that can be achieved. Multiplane TEE prototype probes (Figure 22) that are currently in stages of development include *phased array* as well as mechanical transducers. In the phased array multiplane transducer, a single array of elements is rotated mechanically or by electrically driven motor to provide multiple planes through an arc of 180°. The standard horizontal and longitudinal planes are orthogonal to each other at 0 and 90°, respectively, with intermediate planes between these 2 angles. Graphic display of the angle of rotation is available on the screen.

The perceived benefits of the multiplane TEE

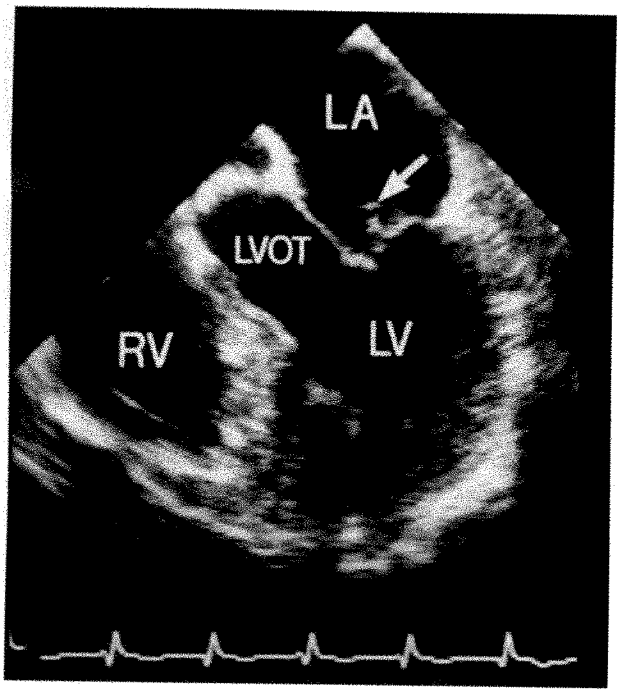


FIGURE 19. Still frame from a patient presenting with a new murmur, hypotension and renal failure following acute inferior myocardial infarction. Four-chamber view in the horizontal plane shows a torn papillary muscle (*arrow*), flailing into the left atrium (LA). LV = left ventricle; LVOT = left ventricular outflow tract; RV = right ventricle.

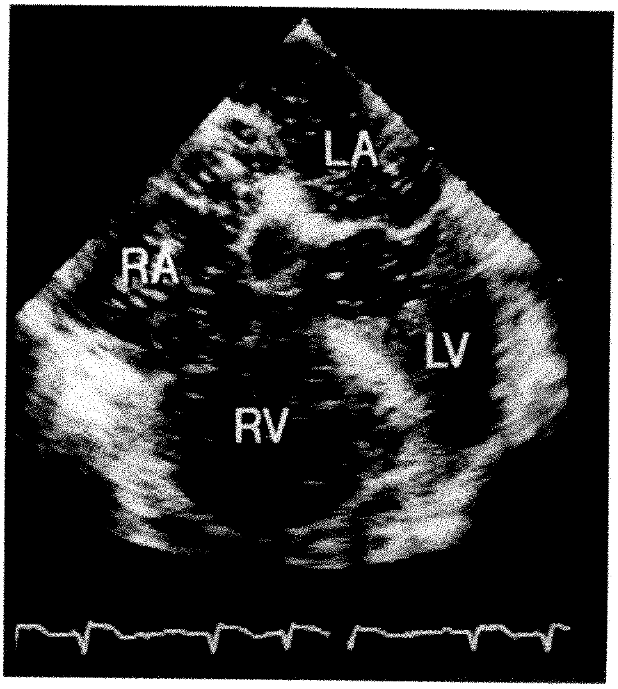


FIGURE 20. Still frame from a patient with persistent hypoxemia following acute myocardial infarction. The frame was taken following injection of agitated saline through a peripheral vein and demonstrates a large right to left shunt. The right-sided chambers are enlarged, with the bulge of the atrial septum toward the left. RA = right atrium; RV = right ventricle; LA = left atrium; LV = left ventricle.

probe from one group of investigators included visualization of precisely aligned short- and long-axis views of the aortic valve, long-axis imaging of the proximal portion of the ascending aorta, visualization of the right ventricular outflow tract, and improved recognition of the spatial patterns of color Doppler jets.[42] Multiplane TEE has been utilized to estimate the aortic valve area (planimetered) with a sensitivity of 94% and specificity of 92%.[43]

Additional perceived benefits of multiplane transducers include fine tuning anatomic abnormalities, better visualization of prosthetic perivalvular regurgitant jets, potential for improved semiquantitation of regurgitant lesions, accurate alignment of continuous wave Doppler beam to obtain accurate hemodynamic information, improved localization and characterization of masses or tumor, and the potential for 3-dimensional reconstruction of structures such as the mitral annulus, atrial septum, aorta, mitral valve, and the left ventricular outflow tract.

Disadvantages of the present multiplane transducers include the size of the transducer tip (16 mm), which makes introduction of the probe difficult. In our early, initial experience with 2 prototype multiplane TEE transducers, the examiners had difficulty in introduction of the probe in 3% of patients. The multiplanar transducer could not be introduced in 3% of patients, whereas a standard biplane transducer could be introduced in these same patients. The large size does pose problems and may limit acceptability of the technology.

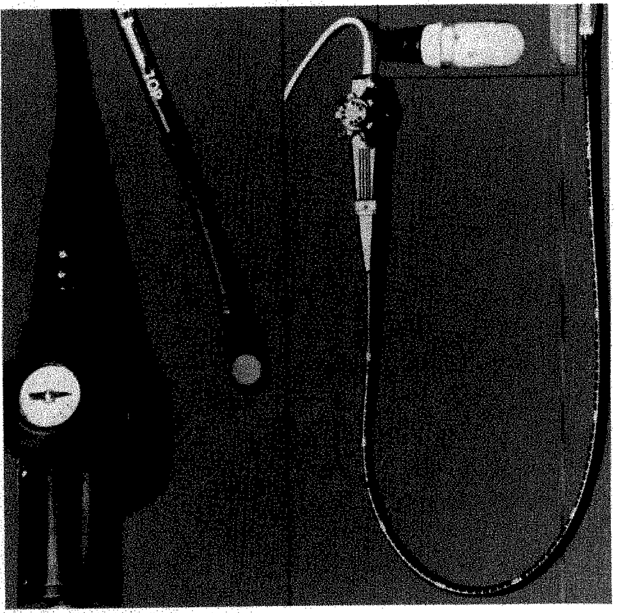


FIGURE 22. Prototype multiplane transesophageal echocardiographic (TEE) probes. Mechanism to rotate the array is located on the handle but can be via an electrically driven motor (*left*) or manual rotation (*right*). Both of these probes use phased array technology.

The reliability of the transducers needs to be tested. Since the transducers have an intricate mechanism inside the housing for rotating the array, it is clear that longevity of the mechanism will need to be evaluated in depth. The additional cost of multiplanar transducers will have to be offset with reliable, long-lasting transducers as well as additional clinical benefits to make the technology a viable option.

The issues of size and improvement in image quality are areas requiring intensive research and development. Image orientation and anatomic correlations are somewhat complex with multiplane TEE, and the learning curve may be longer. The examination time for a complete multiplane examination is longer than single or biplane examination, partly because of the unfamiliarity with anatomy. Image display, so as to reap that maximum benefit of the transducer, remains an elusive goal and is largely dependent on digital technology. It appears that if one were to display the images sequentially, the contiguity of structures would be better appreciated by the examiner as well as the nonechocardiographer viewing the studies.

Another important development in the field of TEE is the availability of wide-field imaging. Early experience was obtained using off-line, computer-reconstructed images (Figure 23).[44] A prototype annular array transducer has been utilized clinically to provide real-time wide-field TEE images.[45] This technology will provide an additional boost to the field of TEE and permit better depiction of contiguous structures. Limitations to the real-time "panoramic" TEE include frame rate compromise with a wider field of view, suboptimal quality images, and a probe size at present that does not allow imaging in children.

Digital technology: There is very little doubt that one of the major advances in the field of echocardiography is going to come with the incorporation of digital technology. The ability to archive and retrieve images becomes easy once data are stored in a digital format. Image manipulation such as placing serial studies side by side to look for subtle or not so subtle changes or comparing studies before and after intervention or thrombolysis are all feasible with digital storage and archiving of images. Multiplane imaging can be readily appreciated if a sequence of images is displayed contiguously. Image transmission from remote sites to tertiary care centers for second opinions, or as a form of service to understaffed hospitals and clinics, becomes a reality with the advent of digital imaging, fiberoptic networks, and availability of very small aperture (VSAT) satellite technology. The advances in TEE will be not only in the area of transducer technology, but also in the area of digital imaging. One can envision a day, not too long in the future, when tissue characterization, on-line 3-dimensional reconstruction, and contrast-enhanced imaging will all be feasible because of advances in the field of digital imaging.

Three-dimensional reconstruction: TEE, especially multiplane TEE or wide-field TEE, lends itself to 3-dimensional reconstruction. There is a paucity of data in this field, insofar as on-line, real-time, 3-dimensional reconstruction is concerned. However, several groups are working in this area. The year 2000 should see their work come to fruition, with availability of the technology for clinically useful indications.

Training: Training guidelines have been recently established by the American Society of Echocardiography (ASE). It is clear that TEE should be performed by a physician only, and also that the physician must have sufficient knowledge of echocardiography. However, the specific details about training, where to train, and number of examinations required for maintaining competence all need to be delineated.

At our own institution, TEE is performed by trained echocardiographers with at least Level II training in echocardiography.[46] Level II training involves the performance and primary interpretation (with proper supervision) of 300 transthoracic echocardiographic examinations over a period of 6 months, or achievement of the equivalent level of experience. Training in the introduction of the probe is obtained in the gastrointestinal endoscopy suite under the tutelage of an endoscopist. At least 25–40 introductions are performed by each echocardiologist before being considered accomplished in the technique. Manipulation of the transducers is accomplished by performing supervised TEE studies, and at our institution this means approximately 20 examinations.

Training of allied subspecialties such as anesthesiology, surgery, and critical care is dependent on whether the physician is going to function as the primary operator in the diagnostic or monitoring part of the TEE examination. We believe that if physicians without background level II training in echocardiography are to embark on utilization of TEE, they must first acquire this training. Hence, anesthesiologists, cardiac surgeons, and critical care specialists need to undergo basic echocardiography training prior to learning the interpretation of TEE or even the procedure of TEE. If the desire to learn TEE is for the purpose of monitoring left ventricular function, an abbreviated training schedule that does not require basic level II echocardiography training may be sufficient. The availability of a trained echocardiologist to help interpretation in difficult situations is recommended.

The issue of how many studies, how often, are needed to maintain competency remains unanswered at this time. The question has been addressed in part by the recently published ASE training guidelines.[47] Societies such as the ASE and American College of Cardiology will have to

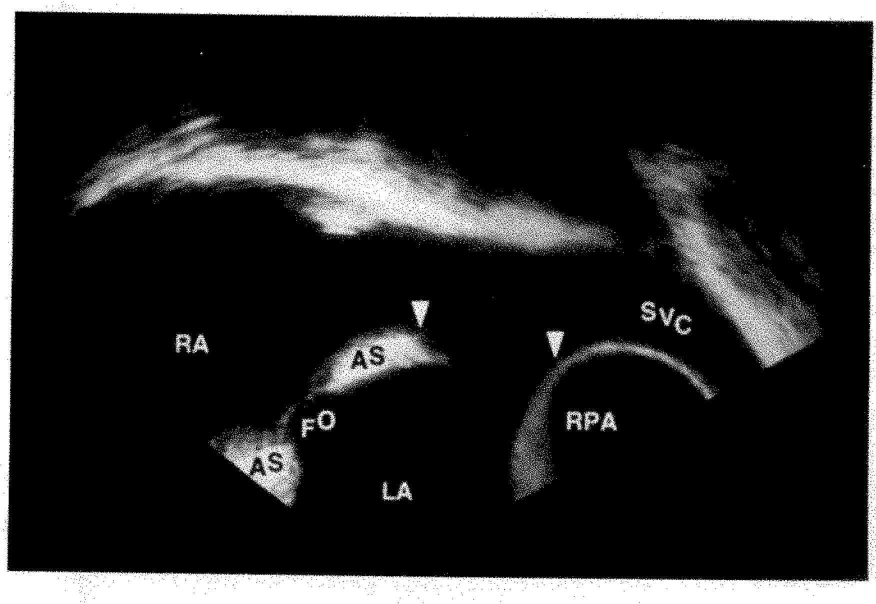


FIGURE 23. Wide-field imaging in a patient with sinus venosus atrial septal defect (*arrows*). The wide-field of view provides a panoramic image as shown here, with the visualization of the superior vena cava (SVC), atrial septum (AS), valve of the fossa ovalis (FO), left atrium (LA) and the right atrium (RA), all in 1 view.

issue guidelines rather than have it thrust on us from the federal government or third-party payers.

REIMBURSEMENT

In the era of cost containment, it is natural that each new technology is viewed as being an additional cost to the total health-care spending. However, TEE clearly stands out as being a poorly reimbursed procedure considering the fact that this is a physician-intensive procedure and provides clinically relevant data in a subset of patients that then obviates the need for additional testing. Reimbursement needs to be set according to the time spent by the physician, since the general direction of reimbursement in the field of medicine is headed in that direction with the implementation of resource-based relative value scale. Legislative bodies will need to embark on this course for determining the appropriate level of reimbursement for outpatient TEE as well as intraoperative TEE.

CLINICAL INDICATIONS

It has been amply demonstrated that TEE is superior to TTE in detecting various cardiovascular abnormalities. However, the improved sensitivity of this technique should not be translated into less emphasis for TTE. Optimal utilization of TEE relies on better understanding of capabilities and limitations of TTE. For now, TTE should remain as the primary echocardiographic examination. The burden is on us to identify clinical settings where TEE provides additional data that will have a direct impact on the process of clinical decision-making and improve patient management and delivery of quality care.

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Discussion III: Transesophageal Echocardiography

Dr. Anthony DeMaria (Lexington, Kentucky): The presentations on transesophageal echocardiography (TEE) have brought up a few questions. Now that biplane probes are widely available, in order to overcome the constraints against imaging the esophagus, is it essential to proceed with Omniplane? Are we likely to diagnose more accurately with an Omniplane probe?

Dr. Christopher Appleton (Tucson, Arizona): We have not had experience with Omniplane probes, but the biplane probe has certain features I would like to see improved, particularly in imaging aortic valves or vegetations. Also, it would be beneficial to know what you are seeing when you are cutting tangentially across the valve leaflet or the floor of a leaflet. That is one area where the ability to make a small manipulation in the probe would clarify an angulation problem. It used to be a big problem with monoplane probes, but sometimes it is still a problem with a biplane probe.

Dr. Harold Rakowski (Toronto, Canada): We do biplane probe studies exclusively, and we will not know the full potential of the new Omniplane technique until we have had experience with it. I think it is possible to speculate that with Omniplane, assuming that the probe size and image qualities are adequate, it will be possible to get additional anatomic information for diagnosis in selected cases. The greatest application, however, may lie in the better ability to quantitate gradients; for example, where you can line up the continuous wave beam more parallel to blood flow. There are still problems in achieving that with biplane. Certainly, for 3-dimensional reconstruction to be of clinical benefit, it will only happen with an Omniplane-type probe.

Dr. William Jacobs (Maywood, Illinois): We have found biplane imaging to be reliable and would not go back to a single plane, although we have never used a monoplane and biplane sequentially on any patients. A multiplane probe might make the examination faster.

Dr. DeMaria: Traditionally, the more views we take, the longer it takes to get them.

Dr. Pamela Douglas (Boston, Massachusetts): The increment from biplane to Omniplane is going to be much less than that from monoplane to biplane. I think it may be possible to see certain areas more easily with an Omniplane probe. There may be an eccentric mitral regurgitation jet or a small vegetation that you do not see with a biplane probe, and it may require a longer time to manipulate. However, I do not believe that you would overlook these areas with careful biplane examination.

Dr. DeMaria: Is the consensus that with Omniplane there may be only a relatively small incremental gain?

Dr. Douglas: Relatively small, but 3-dimensional reconstruction is really only useful with the multiplane technique.

Dr. Nelson Schiller (San Francisco, California): Before we switch from biplane to Omniplane, assuming that biplane is 100% successful, there are some points we need to keep in mind. Studies take longer with biplane but, more importantly, the number of crystals that you use will decrease. This has been true with multiple intubations that we have done recently in patients. In some of the patients whom we examined, we missed vegetation or a certain structure. When the patients went to the operating room, or when we used a single-crystal, single-plane, high-resolution instrument, we immediately saw what we had missed. I want to caution that by slicing 2 ways, getting a lot of contrast resolution, and cutting down the actual grade scale in resolution, you may be paying a higher price in certain cases.

Dr. DeMaria: Good point. Have you gone back to doing monoplane studies?

Dr. Schiller: No, only in cases of resolution drop. I encourage the development of the 64 × 64 element, and I have heard that the 128 × 128 element biplane may solve the resolution problem. However, at the moment our first prototypes are 48 × 48 element.

Dr. Natesa Pandian (Boston, Massachusetts): If we were to compare 2 images side by side, 1 from the 64 × 64 element biplane probe and the other from the 64-element single-plane probe, they would not appear to be different. One may be only slightly clearer.

Dr. Schiller: I would not expect that they would.

Participant: I thought I would sound a word of caution. It is premature to make long-term judgments about the image quality of the Omniplane probe. I agree with what has been said about biplane probes. A diagnosis can be made in most cases with a monoplane probe, but I think a biplane probe would be better. From the little experience I have had with multiplane probes, this is ultimately going to prove to be true.

Dr. Schiller: A system that we have worked with, called the Hitachi System, actually manages to use a simultaneous biplane that achieves almost the same results. It is very surprising that they have accomplished this with such a small probe. Although it is faster and a real improvement to have both techniques at the same time, there is a problem with resolution.

Dr. Michael Quiñones (Houston, Texas): Is it as good as the other techniques that we have discussed?

Dr. Schiller: There have been some problems. It has wonderful context and the images look good, but there is a problem with the small vegetations.

Dr. Douglas: TEE is not exclusively a diagnostic tool. Many TEE exams are being used for intraoperative monitoring as well. In some cases all that is needed is a single plane in the stomach, looking at the short axis. In this case, there is no real advantage to the additional planes.

Dr. Randolph Martin (Atlanta, Georgia): Biplane clearly adds increased diagnostic information. For example, in the ascending aorta algae appendages can often be visualized better. The real difficulty with TEE is training in image recognition, because we do not build up images at the same rate as we do with transthoracic imaging. I think this is another issue that we, as interested users, must face because a mistaken diagnosis in single plane gets stepped up a whole level in biplane.

Dr. Rakowski: Although TEE is a promising technique, most of us are only using it in 4–8% of all patients. We can discuss its potential applications, but we are very selective in how we use it. Is this technique going to become a more of a mainstream procedure, and will we ultimately use it in 25%, 50%, or 75% of the patients we study? We should discuss just how practical it will become by the year 2000. Is it likely that technology will advance so that we can miniaturize the TEE and it will become the mainstay of the echocardiology laboratory rather than the exceptional test for special cases?

Dr. DeMaria: Miniaturizing the components and dealing with the constraints of the esophagus are two areas we still need to overcome in popularizing this technique.

Dr. Appleton: I have noticed how little Doppler we use on TEE. We use it almost exclusively for imaging, and, except in rare cases, we always do a transthoracic study on a TEE unless it is an emergency study. I have never found a study where the deceleration time of the mitral valve was the same as it was transthoracically. My interpretation of this fact is that there are alignment problems with TEE because the valves just are not the same as with the transthoracic studies.

Dr. Jacobs: I think that we would probably use TEE more for the unsatisfactory transthoracic echogram if it were easier to pass the probe, and possibly if it did not require a tranquilizer for the patient. If the probe were designed to be more like an esophageal bougie so that it could be used with the patient sitting vertically, we could do the examination faster and the patient would recover more quickly.

Dr. Douglas: This is also a manpower issue. We need to compare how much time we spend doing a TEE versus how much time we spend interpreting a transthoracic echocardiogram.

Dr. Schiller: Several issues were mentioned that the panel might address. First, I do not believe we can see the effects of TEE most of the time. No matter how many elements are added, the esophagus is in the wrong place and we are missing apical infarctions. I think it is a major issue, particularly in the operating room where I would like to see more surface images over the apex being performed. From what I have seen on most TEE images, we are nowhere near the apex.

Dr. DeMaria: I agree with you, but I think there is a better chance of getting down deeper and closer to the apex with Omniplane than with a single plane.

Dr. Bijoy Khandheria (Rochester, Minnesota): I think the apex can be seen with the biplane technique if it is used properly. However, I do think Omniplane allows you to see the apex more frequently.

Dr. Quiñones: We see an apex 100% of the time in a 4-chamber view with a transducer on the apical input, but we know now that it is a pseudo-apex and not a true apex.

Participant: The esophagus is positioned in such a way that in most cases we cannot get the beam at an angle that will go through the apex, unless the heart is extremely vertical.

Dr. DeMaria: How small must the transducer be to really extend the applications of TEE?

Participant: It has to be nasogastric tube size with good image quality. It may not be currently possible, but there are potential solutions. If we are going to use TEE for contrast, for 3-dimensional reconstruction, or for mainstream echocardiography, the transducer clearly must be smaller and maintain good image quality.

Dr. DeMaria: To obtain ultrasonic penetration, there is a minimum energy level to which you can tune the frequencies, and within that frequency range, you must use a certain size transducer. That is a formidable problem.

Participant: There still must be contact with the esophagus, which sometimes is not possible with the smaller transducers.

Dr. DeMaria: One way to solve this problem is by putting balloons on the ultrasonic transducer, so that the balloon can be inflated while you are maneuvering the transducer and thus at least approach the wall of the esophagus.

Participant: A pertinent subject that has not been discussed is the matter of reimbursement, which ties into the time issue. I would ask the panelists for their opinions on the time and reimbursement issues.

Dr. Douglas: The time issue obviously varies depending on what is being done. We have third-year fellows who do much of the setup—for example, putting in the intravenous line—so it is less time-consuming for us, but they still spend 1–2 hours with the patients.

Dr. Jacobs: At our institution, a third-year fellow does the brief workup and spends perhaps 30 minutes more with the patients than I do. If the resident is just learning, I may spend an hour with the patient. Otherwise I spend about a half hour.

Dr. Rakowski: We perform TEE in the echocardiography laboratory, rather than in a special care area, and we schedule them at the same frequency that we do conventional echoes. We have a third- or fourth-year fellow doing most of it, and the staff person basically comes in for the key part, the distal anastomosis. In terms of how to handle the operating room and the catheterization laboratory, the only way we can cope with the uncertainty as to when they are ready is to hard wire both places to the echocardiography laboratory. That way we have both video and audio communication. In terms of reimbursement, anything that we add to the procedure will probably not be considered reimbursable.

Dr. Appleton: We fit the TEEs into our regular schedule and adhere to the time frame with help from the fellows. Unfortunately, we lose time going to the operating room to perform additional studies. We perform them when the patient needs them, but we discourage the practice for routine use because it requires a tremendous amount of time. If it is really necessary for patient care, we fully support the extra measures. However, we have not encouraged it because we do not have the volume to make it cost effective.

Dr. DeMaria: What you mentioned certainly has implications concerning the issue raised about whether TEE would ever become the primary imaging modality. With the time frame and cost limitations we have now, it does not seem very likely.

Dr. Morris Kotler (Philadelphia, Pennsylvania): I want to comment on the importance of having an echocardiologist go to the operating room in certain situations. In terms of critical management decisions, there have been times when being on the site and interacting with the surgeon really changes the balance in intraoperative management for patients. For the first time, cardiologists have had a window of access into intraoperative and early perioperative management of patients.

Dr. Douglas: I would agree that if it is a diagnostic study, there needs to be an attending cardiologist. However, if it is a routine monitoring study in the operating room, then a well-trained anesthesiologist can do the procedure.

Dr. Rakowski: If you have a well-trained fellow and a video link to the operating room, you can then be in communication without being physically present. If the images are adequate, you can let the operating room staff know. If they are not, then you can go down and assist.

Dr. Kotler: I would like to ask the panel their experiences with heart attack, especially in the aorta and right atrium. What has the experience been and have there been any false-positive diagnoses?

Dr. Douglas: At times I think we see phenomena that we do not specifically label. However, I do not know of any time that we have made a false diagnosis and that the patient later had an anatomic confirmation at surgery.

Dr. Quiñones: Regarding state-of-the-art and future applications of TEE, I would like to ask the panelists if they foresee specialized TEE machines and systems being used in the operating room, and what subtleties are involved?

Dr. Schiller: Installing a machine in the operating room, one that is served by a central machine from several lines, is something that the echocardiography industry would hesitate to do because they could lose economically. They might have to reduce their prices by miniaturizing the components.

Dr. Quiñones: Are you saying that whatever happens could be determined by marketing considerations, rather than what the medical community demands?

Dr. Schiller: I am afraid that is the way it is.

Participant: Unequivocally, I think there will be small machines or TEE machines dedicated to the operating room, primarily used by cardiac anesthesiologists and cardiac surgeons.

Participant: This is also a time and training issue. The younger cardiac surgeons are perhaps more enthusiastic. They want an echocardiogram on every patient and as technology improves, the demand will increase for small machines in the operating room.

Dr. DeMaria: I think you are right. Cardiologists have to be educated. We started to provide them with useful information and then we had to educate them as to what the equipment can and cannot do.

Dr. Douglas: The issue of what kind of equipment is going to be in the operating room is important because the echocardiography companies are getting resistance from anesthesiologists and surgeons about spending $250,000 for a machine. They are hoping for a trade-off—perhaps price-for-volume.

Dr. DeMaria: There is also the issue of the resource-based relative value scale. Under the rules for Medicare patients, the hospital is not reimbursed more money regardless of whether the patient has had echocardiographic monitoring. Therefore, the hospital must seriously consider whether to purchase equipment that may not increase their reimbursement.

Dr. Alan Pearlman (Seattle, Washington): I believe there is a fundamental dilemma regarding the issue of training. It is not entirely clear to me how a machine could be produced that is cost effective, has multiple applications, and is simple enough to operate by some of the nonechocardiographic experts.

Dr. DeMaria: This is definitely an important issue.

Dr. Harvey Feigenbaum (Indianapolis, Indiana): I have always said that ultrasound is a specialized area and that there should be dedicated cardiac units, radiology units, and obstetric units. The ultrasound companies profit if they can have one machine serve several specialties. That is what they would prefer.

Dr. DeMaria: Don't you believe that hospitals would want to purchase a machine that would satisfy the requirements of radiologists, obstetricians, and cardiologists? I would think that there would be a large demand for such equipment, especially in smaller hospitals.

Dr. Feigenbaum: I cannot make claims as to every small hospital, but there is clearly enough usage so that any middle-sized hospital need not have three different specialists using the same instrument. More often than not, the radiologists will want their own instrument, and the cardiologists also will want their own instrument. Obviously, there must be a limit, but in many hospitals that is the situation.

Dr. DeMaria: Let me ask the panel, what are we going to do about the transient ischemic attack and cerebrovascular accident problem, where we have numerous patients to study, and yet it is not clear what the yield is? Also, even when the yield occurs, what is the relation between their disease and transient ischemic attack or cardiovascular accident?

Dr. Julius Gardin (Orange, California): I think we need multicenter studies to answer that question.

Dr. DeMaria: Let me be more specific. What are your current approaches? Are you doing a TEE on every patient with a transient ischemic attack or cardiovascular accident, without major evidence of cerebrovascular disease?

Dr. Gardin: Of course, we are doing what we are requested to do. My approach is that if there is no evidence of cerebrovascular disease, and they have had the transient ischemic attack, we should be doing a TEE on them. We try to encourage this point of view.

Dr. DeMaria: Even if they have had an excellent transthoracic study?

Dr. Gardin: Yes, because we are looking for the atrial appendage and possibly another mass that may have been missed by a transthoracic scan. In addition, we believe that we get better visualization of the atrial septum.

Dr. Howard Dittrich (San Diego, California): At first, of course, we did every patient we were asked to study because we wanted to perform all the TEEs that we could. Now, we are trying to be more selective, but I think everyone is concerned about patent foramen and similar activity. There is much more now with transcranial Doppler and right-sided injections and positivity after right-sided contrast medium injections. I also think we have to answer this question with an organized study.

Dr. Steven Goldstein (Potomac, Maryland): Some neurologists are much better and more selective in choosing those patients who potentially have clinically embolic strokes. Other neurologists want a TEE for mini strokes and we try to educate them to be more selective. I agree with Dr. Gardin and I think there is a need for a major study in stroke patients. In general, the younger the patient, I think the more legitimate it is to do a TEE.

Dr. Schiller: In our institution, neurology or neurosurgery orders the TEEs and I have had difficulty discerning a pattern. We were coming up with a tremendous number of negative studies, and I have had a feeling that the staff was on the learning curve and would be more selective, which usually results in far fewer studies. What we have now are the surface echoes for contrast for patent foramen ovale (PFO), and the young people who have transient ischemic attacks, particularly after the second or third incident. Neurology is still asking for TEEs in these cases, but I believe they are ordering fewer.

Dr. Arthur Labovitz (St. Louis, Missouri): We examine all patients with unexplained cerebral ischemia. I think several issues are present here. It may be easy to dismiss this condition and say we are not going to have a high yield, but data are available. Several studies have been published where the yield, depending on what is included as a positive finding with TEE, is 40–60%. That, of course, includes the atrial septal aneurysms, the PFO, and spontaneous contrast.

Dr. Pandian: Does it also include mitral valve prolapse?

Dr. Labovitz: No, it does not include mitral valve prolapse. I think it would be an error to ignore the available data that reveal a 2- to 10-fold increase in such findings in patients with unexplained cerebral ischemia versus the rest of our population.

Dr. DeMaria: Can these patients be treated with anything other than anticoagulants?

Dr. Labovitz: I think the important issue is whether antithrombotic therapy, such as aspirin or warfarin, makes a difference in these patients. Clearly, there is a high recurrence rate. If you examine the prognostic value of TEE, patients with an index event who have a PFO or atrial septal aneurysm have nearly a 20% recurrence rate in the first 2 years. I would think that antithrombotic therapy makes an impact. We could give them all warfarin, but we know that warfarin is not without morbidity. On occasion, we also have findings such as thrombi, spontaneous contrast, or tumor. We need to weigh these issues in conjunction with the type of therapy administered.

Dr. DeMaria: If you have a negative study, do you advise the neurologist not to administer warfarin?

Dr. Labovitz: Yes, if we have an absolutely negative study. I have the data on the recurrent event rate in that group, and it is low.

Dr. Kotler: Is this in the presence of atrial fibrillation?

Dr. Labovitz: No, atrial fibrillation is a separate issue. We have examined a group of patients with atrial fibrillation and unexplained cerebral ischemia versus those with sinus rhythm. The atrial fibrillation group, as might be expected, has a slightly higher incidence of spontaneous contrast, but a lower incidence of PFOs.

Dr. Kotler: If you have a negative TEE study and chronic atrial fibrillation in a patient who has established stroke, to me this implies that you will continue anticoagulation therapy.

Dr. Labovitz: As you know, the studies have shown that antithrombotic therapy impacts on the incidence of recurrent stroke in this group. However, that is still <10% per year. We do not know that the other 90% of patients are at low risk and may not need antithrombotic therapy.

Dr. Sanjiv Kaul (Charlottesville, Virginia): At our institution every stroke patient has an echocardiogram. It is part of the protocol. On all those echoes, we have used transthoracic, and now they are doing TEEs. With a selected patient group, you have a 40% incidence of recurrence. With TEE the same thing occurs: I do not find abnormality with unselected patients. If the patient is fibrillating, is known to have mitral valve disease, and has cardiomyopathy, I know why the patient is having the embolic event. However, in totally unselected patients, patients with a stroke or a transient ischemic attack, my yield is very low.

Dr. DeMaria: About 44% of Dr. Kaul's increased yield was on spontaneous contrast. What about patient selection in infectious endocarditis? Does every patient who has infectious endocarditis need a TEE, even if they make excellent transthoracic images and the vegetations are seen?

Dr. Gardin: I have seen data where it makes a big difference, but personally I do not believe that a TEE is needed if they have an excellent transthoracic echo. However, particularly in cases in which there is a huge index of suspicion of bacterial endocarditis, complications, or you just do not see anything on the transthoracic echocardiogram, you need to select the patients in whom you will do a TEE.

Dr. Dittrich: We have a large population of patients at risk for endocarditis, and we probably see a skewed population with many vegetations. Basically, I agree with Dr. Gardin, we do not routinely do a TEE unless there are specific problems. Obviously, prosthetics is a different matter, and we have had some success with TEE in aortic prostheses.

Dr. Goldstein: I also agree that TEE, although potentially educational and revealing, is not necessary for every patient with endocarditis. If there is no hemodynamic problem, the patient is responding well to therapy, and especially if the lesion is clear cut, well seen, not near an annulus, or you are not concerned about a potential complication, I do not believe it is necessary. However, it has been useful.

Dr. Schiller: Based on the fact that I see a lot of endocarditis in my own practice, and because the procedure helps me to decide if I should treat the patient on an inpatient or outpatient basis and for how long, I would tend to do TEE on almost every endocarditis patient I see. I highly recommend it.

Dr. Quiñones: If the transthoracic study is positive, then you already have a high-risk patient. It is in those high-risk patients, when you do a TEE, that you find other important associated problems.

Dr. Richard Meltzer (Rochester, New York): If a patient has sustained positive blood cultures, multiple times from multiple sources with no definable secondary source of infection, they have to be treated for endocarditis no matter what our experience is with the sensitivity of TEE.

Participant: What if you have a positive transthoracic study and a positive blood culture with mitral vegetation and you perform a TEE?

Dr. Schiller: If the vegetation is <10 mm, then these patients are ideal candidates for immediate home therapy. It involves 4 weeks of therapy, most of which can be at home with intravenous lines and nurses. I am very aggressive about that. If someone has a nearly destroyed valve, bulky vegetations, embolic potential that is high with vegetations >10 mm, or especially if they have multiple sites of abscess, I will keep these patients in the hospital. I will monitor them and may look for a heart block. If something is obvious on the transthoracic study, you will see more on the TEE.

Dr. David Skorton (Iowa City, Iowa): Home therapy, while a matter for debate, is unquestionably a frequent practice. To determine who would require an echocardiogram would depend more on the organisms involved and how sick the patient was. With a negative transthoracic echo, you should absolutely do a TEE if there is any suspicion because of its relatively high sensitivity.

Dr. DeMaria: In terms of prosthetic heart valves, is it our assumption that the panel is doing studies primarily in symptomatic patients, patients suspected of having dysfunction, or have you yet moved to the point where you are performing routine TEE?

Dr. Gardin: No, we have not moved to that point yet. I suspect if economic factors are not pressing, we probably will not for some time.

Dr. Goldstein: If there is no clinical suspicion of a problem with a prosthetic valve, in my opinion TEE is not needed.

I would like to ask the panel about the competing technology for TEE, specifically magnetic resonance imaging (MRI). What direction is MRI taking? Will it compete with TEE or are they going to be completely different?

Dr. Nathaniel Reichek (Philadelphia, Pennsylvania): It depends on the area. One factor that is going to impact on technique in the next 3 years is real-time MRI. It is just beginning to disseminate and it promises to be a powerful technique. I believe that, like all other areas where MRI and echocardiography have been applied, there is not going to be a conflict. They are complementary in that they address different sectors of the spectrum. It is likely that MRI will have a better track record and definitive answers to certain kinds of questions over the coming years, but I really do not see it having an effect on the pattern of utilization of echocardiography.

Exercise Echocardiography

Thomas Ryan, MD, and Harvey Feigenbaum, MD

Exercise echocardiography is a versatile, noninvasive diagnostic test that involves the recording and interpretation of 2-dimensional echocardiograms prior to, during, and after exercise. By analyzing and comparing wall motion at each stage, a prediction about the presence or absence of coronary artery disease can be made. The development of a wall motion abnormality is both sensitive and specific for the presence of a significant coronary stenosis. Changes in regional systolic function during exercise enable the clinician to distinguish between infarction and ischemia. Thus, the test yields information on the presence, extent, severity, and location of coronary artery disease. Echocardiography can be adapted to almost any form of stress, although treadmill or bicycle exercise are most commonly employed. An advantage of bicycle stress echocardiography is the opportunity to image during exercise, rather than relying on postexercise recording. This contributes to enhanced sensitivity, although false-positive results may increase due to the difficulties of analyzing wall motion during strenuous exercise. Exercise echocardiography increases the diagnostic accuracy of stress testing in a manner similar to radionuclide perfusion imaging. It is particularly useful in the setting of an ambiguous stress electrocardiography (ECG) or when a false-negative or false-positive result is suspected. It has been successfully applied to patients following revascularization and yields useful prognostic data in a variety of clinical situations. Exercise echocardiography is being increasingly utilized as a safe and accurate test in patients with known or suspected coronary artery disease.

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Over the past decade, exercise echocardiography has developed into a clinically useful tool, providing prognostic and diagnostic information on patients with known or suspected coronary artery disease. The test is fundamentally based on 3 assumptions: (1) that the induction of ischemia will result in an area of left ventricular (LV) dyssynergy, (2) that such regional abnormalities developing during exercise are relatively specific for ischemia, and (3) that changes in regional wall motion can be recorded accurately using 2-dimensional echocardiography.

Because decreases in wall thickening and endocardial excursion are early and sensitive manifestations of ischemia,[1,2] the first 2 assumptions appear well founded. It is only in the past several years, however, that convincing evidence has accrued to support the third assumption. There is now a growing awareness that the addition of echocardiographic monitoring to routine exercise testing enhances the test's ability to detect, localize, and quantify myocardial ischemia. The purpose of this review is to summarize this body of evidence supporting the clinical application of exercise echocardiography.

AN HISTORICAL PERSPECTIVE

The earliest report on the use of ultrasound to monitor LV wall motion during exercise was published in 1970.[3] Later reports, using M-mode echocardiography, provided insight into various aspects of cardiac function and physiology.[4] The ability to record LV dimensions and to detect changes in chamber sizes and shortening fraction made exercise echocardiography a valuable tool for understanding exercise physiology.[4,5]

The use of exercise M-mode echocardiography for the detection of ischemia was first reported in 1979.[6,7] Although the demonstration of transient wall motion abnormalities was exciting, the inherent limitations of the M-mode technique precluded

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clinical application.. The use of 2-dimensional echocardiography in conjunction with stress testing was also first reported in 1979.[8] The advantages of this imaging modality were obvious, although widespread use was hampered by image quality and the difficulties of videotape analysis. Successful imaging was possible in only 70–80% of patients[9–13] and overall image quality was marginal. This factor, combined with the respiratory interference inherent with exercise, made videotape analysis of the early exercise 2-dimensional echocardiograms quite challenging. These obstacles, coupled with the emergence of radionuclide scan techniques to assess ischemia, discouraged widespread clinical acceptance and relegated exercise echocardiography to the research laboratory.

In the mid 1980s, 2 occurrences contributed to a resurgence of interest in exercise echocardiography. First was the general improvement in image quality attributable to various technologic advances in ultrasound equipment. Imaging success rates improved to an acceptable and competitive level and this trend has continued to the present. Today, success rates of 90–95% are the norm.

The second factor that propelled stress echocardiography into the clinical arena was the development and application of digital processing techniques to echocardiographic imaging.[14] This technology allowed the conversion of analog ultrasound information to digitized images. Initially, this was accomplished "off-line" by processing of videotaped records.[15] Later, "on-line" methods became available, permitting digitization of ultrasound data directly from the scan converter. Through the implementation of these methods, exercise echocardiography became a more accurate, feasible, and convenient diagnostic test. The impact of these innovations was profound and led directly to a dramatic increase in the availability and acceptance of the technique.

TECHNICAL CONSIDERATIONS: EXERCISE METHODOLOGY

In practice, echocardiography can be adapted to many forms of stress. Most often, 2-dimensional echocardiography is combined with either treadmill or bicycle (supine or upright) exercise. In all cases, the goal is to record and compare LV wall motion before, during, and after exercise. With treadmill testing, imaging is only feasible before and immediately after exercise. Although attempts have been made to develop devices to permit imaging during treadmill exercise,[16] most investigators have relied exclusively on immediate postexercise recording.[10,13,17] Thus, wall motion abnormalities must persist into early recovery to be detected. Although this occurs in the majority of patients, "rapid recovery" of dyssynergic segments can lead to false-negative results.[18] Wann et al[8] described occasional cases of postischemic hyperkinesis in areas rendered akinetic during exercise.

TABLE I Clinical Features in Patients with Wall Motion Abnormalities That Persist into Recovery Compared with Those Exhibiting Rapid Recovery

	Persistent (n = 22)	Rapid Recovery (n = 7)
Exercise duration (sec)	247 ± 119	266 ± 124
Maximum heart rate (bpm)	138 ± 21	138 ± 18
Patients with angina (%)	38	71
Patients with collaterals (%)	29	57

Adapted from *J Am Soc Echo*.[21]

Despite the theoretical limitations of relying on postexercise imaging, the technique is currently enjoying widespread application for a variety of reasons. Because treadmill testing is the most widely available form of exercise testing in this country, it is generally more expedient to adapt stress echocardiography to an established treadmill laboratory. Also, by avoiding the need to image at peak exercise, both performance and interpretation of the test are simplified. Finally, monitoring the rate and completeness of recovery of wall motion abnormalities may provide additional diagnostic or prognostic information.[19]

Using bicycle exercise, imaging throughout the exercise protocol is feasible. During supine bicycling, all views can generally be recorded, whereas in the upright posture imaging is limited to the apical and subcostal windows.[20] The ability to image at peak exercise enhances the sensitivity of the test to detect transient ischemia.[21] However, the clinical importance of peak exercise imaging has not been proven, and there are disadvantages to the bicycle technique. In addition to the greater complexity of bicycle compared with treadmill exercise echocardiography, the level of stress obtained is sometimes lower. Elderly patients, in particular, are often incapable of exercising adequately in the recumbent position.

The diagnostic accuracy of peak versus postexercise imaging has been compared in one study using upright bicycle exercise.[21] In this series of 96 patients, 29 developed an induced wall motion abnormality (Table I). These transient wall motion abnormalities were more frequent at peak exercise, resulting in a higher sensitivity for the detection of

TABLE II Advantages of Digital Imaging

- Side-by-side display of rest and stress images allows subtle differences to be detected, improving sensitivity.
- Acquisition time is reduced because only a single cardiac cycle is required of each view to construct the cine loop.
- By selecting the cardiac cycle to be used for the cine loop, respiratory interference is minimized.
- Digital techniques facilitate storage, interpretation and retrieval of the exercise echocardiograms.
- The convenience of the method enhances teaching and communication with referring physicians.

angiographic coronary artery disease. Of the 29 new wall motion abnormalities, 10 had resolved completely at the time of postexercise imaging. The reasons for this phenomenon are unknown, although some conclusions can be drawn. Intercoronary collaterals were more common in patients demonstrating rapid resolution of wall motion abnormalities, and these patients were also more likely to experience angina during the stress test. The authors concluded that well-developed collateral vessels may lead to rapid resolution of wall motion abnormalities and may account for some cases of false-negative postexercise echocardiographic results. Duration of ischemia may also be a factor. Because the rate of recovery of systolic function is directly related to the duration of ischemia,[22,23] rapid recovery would be more likely in patients who stop exercising earlier in the course of ischemia. Patients in whom ischemia was associated with chest pain may have their test terminated earlier than those who fail to manifest angina. This could partly explain the increased likelihood of rapid recovery in patients with angina.

There are few data directly comparing these different stress methodologies. Some reports have suggested a slightly higher sensitivity, but lower specificity, using bicycle versus treadmill exercise.[24] Most recent studies have confirmed that both techniques are feasible and provide accurate diagnostic information.[24–28]

In summary, the opportunity to image at peak exercise is an advantage of bicycle exercise. This may contribute to greater sensitivity, perhaps at the expense of lower specificity, for the detection of coronary artery disease. As yet, there are no data comparing peak bicycle imaging to posttreadmill imaging. Because of differences in workload achieved, one cannot assume that postexercise imaging following bicycle and treadmill testing are equivalent. Wall motion abnormalities may persist longer into recovery following treadmill exercise, facilitating echocardiographic detection. Both exercise modalities are currently being used successfully in many laboratories, and as yet there is no compelling evidence that one is clearly superior to the other.

ADVANTAGES OF DIGITAL IMAGING

The field of stress echocardiography has benefitted in recent years from the application of digital recording methods (Table II).[14,15] This technology permits the creation and display of a "cine loop," that is, a series of images (usually 8) played in an endless-loop sequence. By convention, the loop begins with the R-wave and is composed of either the entire cardiac cycle or, more commonly, only systole.

Once digitized, the images can be displayed in a variety of ways. For example, a quad screen display can be created in which each quad is an 8-cell sequence, synchronized to the R-wave. This format allows analogous views at rest and with stress to be displayed side-by-side. Such a display greatly facilitates comparison of baseline and stress images. This is much preferable to videotape analysis and facilitates detection of subtle differences, thus enhancing sensitivity.

Digital recording also reduces image acquisition time. Since only a single cardiac cycle is needed to create the cine loop, the recording time of each view can be abbreviated. This is particularly important for immediate postexercise imaging, when minimizing recording time is crucial to avoid missing transient wall motion abnormalities. The problems of respiratory interference can also be partially eliminated through the use of these methods.

Digital techniques also contribute to the convenience of stress echocardiography. Storage, retrieval, and display of stress echocardiograms are favorably affected. An entire stress study can be stored on a single floppy disk. The images can be readily recalled, either from the floppy disk, optical disk, or from the computer's hard disk. Teaching and communication with referring physicians are enhanced by these features.

Digital recording is readily adapted to all forms of stress echocardiography and has a favorable impact on accuracy and convenience. The equipment is affordable and can be directly incorporated into the ultrasound machine. Attempting stress echocardiography without the digital recording approach should generally be discouraged.

INTERPRETATION OF STRESS ECHOCARDIOGRAMS

When compared with other stress imaging modalities, an advantage of echocardiography is its ability to record LV wall motion in multiple tomographic planes. By comparing regional wall motion before, during, and after exercise, one can distinguish: (1) the normal hyperdynamic response to exercise; (2) evidence of prior infarction (or perhaps hibernating myocardium), characterized by a stable wall motion abnormality; and (3) evidence of ischemia, identified by the development of a new wall motion abnormality during stress.

In general, the absence of a hyperdynamic response to exercise should be considered abnormal. However, there are several notable exceptions to this rule which must be considered in order to avoid false-positive results. This is particularly true when analyzing postexercise images. In this situation, wall motion that appears normal and unchanged from baseline (but not necessarily hyperdynamic) should be interpreted as "normal." Causes of a lack of hyperkinesis in the absence of coronary artery disease include cardiomyopathy, markedly increased blood pressure, β-blocker therapy, and a low level of exertion.

The development of a new regional wall motion abnormality during or immediately after exercise is quite specific for ischemia. In fact, any degree of deterioration of wall motion should be considered evidence of ischemia, provided that wall motion is normal at rest. Worsening of a preexisting wall motion abnormality during exercise represents a diagnostic dilemma. Although some investigators have considered this an ischemic response, others suggest that it is nonspecific, possibly representing either ischemia or prior infarction.

The uncertainty exists because unfavorable alterations in local loading conditions could lead to a deterioration in regional systolic function in the absence of ischemia. Thus, one of the unresolved issues in exercise echocardiography is how to interpret a worsening wall motion abnormality. Is it possible to detect induced ischemia within an area of prior infarction? A preliminary study has suggested that this may not be feasible.[29] At Indiana University, a hypokinetic segment that becomes akinetic or dyskinetic with stress is labeled ischemic, whereas an akinetic area that worsens with stress is considered evidence of infarction (in which the issue of ischemia cannot be addressed).

Exercise echocardiograms can be interpreted using a variety of qualitative and quantitative approaches. Each interpretive method has its advantages and disadvantages, although all provide useful diagnostic data with an acceptable degree of reproducibility.[30] It should be recognized that a learning curve exists for proper interpretation, and a training period of at least 100 studies may be required before optimal results can be expected.[31]

DIAGNOSTIC ACCURACY OF EXERCISE ECHOCARDIOGRAPHY

The reported accuracy of exercise echocardiography varies somewhat, partly due to differences in technique, patient population, and criteria used to define an abnormal response. Earlier studies reported sensitivities for the detection of coronary artery disease in the range of 50–90%.[8–10,12,17] In this era, prior to the advent of digital imaging methods, adequate images could be obtained in approximately 70–80% of patients. Some studies have included a relatively high percentage of patients with myocardial infarction (MI), most of whom had resting wall motion abnormalities. This tends to inflate sensitivity, since the diagnosis of coronary artery disease is readily apparent by virtue of a baseline abnormality.

More recent studies, using digital technology, have demonstrated higher sensitivity and feasibility (Table III). Armstrong et al[32] examined 123 patients before and immediately after treadmill exercise and stratified the cohort on the basis of prior infarction and extent of angiographic disease (defined as ≥50% coronary artery narrowing). Overall sensitivity was 88% and specificity was 86%. Sensitivity was higher in patients with multivessel disease (93% vs 81%) and in patients with prior MI. This latter result would be anticipated on the basis of resting asynergy. In a subsequent study in which patients with rest wall motion abnormalities were excluded,[33] sensitivity was lower (78%) and specificity was improved. Although the overall accuracy was acceptable, the ability of the test to detect multiple wall motion abnormalities specifically in patients with multivessel disease was limited. Subsequent reports have largely confirmed the overall accuracy of the test and have demonstrated its particular value in those patients with a nondiagnostic stress electrocardiogram (ECG).[34]

As experience grows and technology continues to evolve, accuracy predictably improves. Crouse et al[25] recently reported their experience in 228 patients studied with treadmill exercise echocardiography and coronary angiography. These investigators insisted on the development of hyperdynamic wall motion postexercise to be considered normal—absence of hyperkinesis was interpreted as evidence of disease. Using these criteria, they reported a sensitivity of 97% overall and 100% in those patients with multivessel disease. Accuracy was substantially greater compared with the stress

TABLE III Accuracy of Treadmill Exercise Echocardiography.

			Sensitivity*			
Study	Year	No. Patients	Overall (%)	No MI (%)	Specificity (%)	Success† (%)
Maurer and Nanda[10]	1981	48	86	83	92	85
Robertson et al[17]	1983	30	100	100	75	92
Limacher et al[12]	1983	77	91	—	88	99
Heng et al[16]	1984	47	100	—	93	87
West et al[15]	1985	96	85	—	71	—
Armstrong et al[34]	1986	95	88	80	87	100
Armstrong et al[32]	1987	123	87	78	86	—
Ryan et al[33]	1988	64	78	78	100	—
Sawada et al[24]	1989	38	80	—	94	100
Sheikh et al.[26]	1990	34	74	74	91	100
Crouse et al[25]	1991	228	97	—	64	100

Sensitivity is presented for the entire study (overall) and, when possible, for the cohort of patients without prior myocardial infarction (No MI).
†Percentage of patients in whom technically adequate echocardiograms were obtained.

ECG, and multiple wall motion abnormalities were detected in 93 of 106 patients with multivessel disease. Not surprisingly, specificity was rather low (64%).

No study of comparable size has examined the overall accuracy of bicycle exercise echocardiography. Duchak et al[18] reported a series of 72 patients, all of whom underwent bicycle stress testing prior to coronary angiography. Sensitivity for the detection of coronary artery disease was 94% for the entire group and 88% for the subset of patients with normal wall motion at rest. Of 33 patients with multivessel disease, 28 had either an induced wall motion abnormality or multiple abnormalities at rest. Inclusion of the peak exercise images improved sensitivity by identifying 9 patients with abnormalities not present on the postexercise images. However, 4 of these were false-positive results, which reduced overall specificity to 70%.

Two recent studies have addressed the potential for exercise echocardiography to predict the severity of coronary artery narrowing. Sheikh et al[26] examined 34 patients with single-vessel disease and normal wall motion at rest, using treadmill exercise and coronary angiography. They demonstrated that wall motion abnormalities were frequently associated with stenoses ≥75% (by visual estimate) and were rare with stenoses ≤25%. However, in patients with moderate coronary narrowing (approximately 50%), wall motion response was variable. Using quantitative angiographic techniques, a close correlation between wall motion and minimal luminal diameter was found.

Agati and his colleagues[27] obtained similar results studying 57 patients with single-vessel disease. They correlated several quantitative angiographic parameters with segmental area changes using echocardiography. The severity of coronary narrowing was related to the decrease during exercise of the segmental fractional area change. Although the quantitative echocardiographic approach was effective for detecting severe coronary stenosis, changes in wall motion were variable in patients with less severe narrowing.

These 2 clinical studies confirm the ability of exercise echocardiography to detect severe coronary disease and to provide an estimate of the physiologic significance of the lesion. The consistent observation that wall motion response is variable in the setting of "moderate" disease suggests that the measurement of arterial narrowing is not the sole determinant of inducible ischemia. Thus, changes in wall motion can provide an independent measure to assess the functional significance of "borderline" coronary lesions.

COMPARISON WITH OTHER IMAGING MODALITIES

Several early studies compared exercise echocardiography with radionuclide techniques. Crawford et al[35] examined the ability of bicycle exercise echocardiography and radionuclide angiography to detect changes in ejection fraction during exercise. This was the first study to demonstrate that LV volume and ejection fraction could be measured during exercise using 2-dimensional echocardiography, with acceptable intra- and interobserver variability. For the detection of coronary artery disease, most investigators have found that the 2 tests are comparable.[12,13] At least one study has suggested that exercise echocardiography may be more sensitive for the identification of patients with single-vessel disease,[12] although this has not been a consistent finding.[13] The advantages of exercise echocardiography over radionuclide ventriculography are several. Echocardiography is tomographic rather than planar, thus permitting a more complete assessment of LV wall motion. Because echocardiography is a real-time examination, it allows instantaneous beat-to-beat recording rather than averaging the imaging data over several minutes. Finally, echocardiographic methods are cost effective and totally noninvasive.

Studies comparing echocardiography with myocardial perfusion scintigraphy have generally demonstrated concordant results.[8,10,15,36] The largest series to date, a preliminary report by Haichin et al,[29] examined 145 patients with treadmill exercise echocardiography and single photon emission computed tomography (SPECT) thallium-201 imaging. Agreement as to the presence or absence of coronary disease occurred in 90% of cases. One potential advantage of perfusion imaging may be to detect ischemia within areas of prior infarction. In this study, 15 patients had a "mixed" perfusion defect in an area of resting akinesis. The significance of worsening wall motion in regions of prior infarction has not been carefully investigated with exercise echocardiography. Thus, thallium-201 imaging may be advantageous in this setting.

More recently, Pozzoli et al[37] compared the diagnostic accuracy of upright bicycle exercise echocardiography and technetium-99m MIBI SPECT in 75 patients. Concordance was 88% and both echocardiography and scintigraphy were superior to the stress ECG. Although the 2 tests were equally sensitive for the detection of multivessel disease, echocardiography was significantly less sensitive for the detection of patients with single-vessel disease. The difference could be explained almost entirely by an inability of exercise echocardiography to identify left circumflex coronary artery disease. Although upright bicycle ergometry was used, peak exercise imaging was not performed and this may account for some of the false-negative results.

Thus, exercise echocardiography and perfusion imaging techniques provide similar information on the presence of inducible ischemia or prior infarction. Most studies to date could be criticized because one or the other method is not considered "state-of-the-art." As yet, no large series exists in which both imaging modalities are optimally performed and then correlated with coronary angiography. Despite this, a high degree of concordance has been demonstrated by several investigators. Scintigraphic methods may be advantageous in some situations, such as patients with single-vessel disease or to detect ischemia within an area of prior infarction. Echocardiography is considerably less expensive and more convenient. There is no exposure to radiation and patients are not required to return later for redistribution imaging. Echocardiography also yields ancillary information on valvular and pericardial disease.

TABLE IV Indications for Exercise Echocardiography

- Patients who have had a prior nondiagnostic stress test
- Patients with a high likelihood of a false-positive stress ECG, such as women or those taking digitalis
- Patients with conduction or repolarization abnormalities rendering the stress ECG difficult to interpret
- Patients with a high pretest likelihood of disease in whom the test is done to determine the extent and/or location of ischemia
- Patients who had or will have an intervention to assess the physiologic significance of a lesion or to determine the success of the intervention
- Patients recovering from MI in whom prognostic information is needed

Adapted from a Position Paper of the American College of Cardiology. Approved by the ACC Board of Trustees, October 22, 1989.
ECG = electrocardiogram; MI = myocardial infarction.

CLINICAL INDICATIONS FOR EXERCISE ECHOCARDIOGRAPHY

The improved accuracy and supplemental information provided by exercise echocardiography must be balanced against the added complexity of imaging. Clearly, all stress tests do not require the addition of echocardiographic monitoring. In which situations are the added cost and inconvenience of imaging justifiable? Several studies have addressed this issue and the American College of Cardiology has recently provided some guidelines (Table IV).

It is well established that echocardiography improves the sensitivity and specificity of exercise testing. It also provides information on the extent and location of disease. Thus, to use exercise echocardiography properly one must consider 2 issues: (1) the clinical question that is being asked, and (2) the likelihood that routine stress testing will not provide the entire answer. The most common scenario involves the patient who either has had or likely would have a nondiagnostic stress ECG. In this situation, the inclusion of echocardiography significantly increases the yield of the test.

Armstrong et al[34] demonstrated that the presence or absence of coronary artery disease can be correctly predicted using echocardiography in approximately 75% of patients with an ambiguous or false-negative treadmill ECG. Depending on the population, as many as 60% of patients could be included in this category. Women seem particularly prone to such nondiagnostic results, due to

TABLE V Use of Exercise Echocardiography to Predict Clinical Outcome in Patients Recovering from Myocardial Infarction

Study	No. Patients	Sensitivity	Specificity	Criteria
Jaarsma et al[44]	43	75%	78%	Transient remote asynergy
Applegate et al[45]	67	63	80	New/worse WMA
Ryan et al[46]	40	80	95	New WMA

WMA = wall motion abnormality.

their lower prevalence of disease and increased likelihood of a false-positive stress ECG. Sawada et al[24] examined the utility of stress echocardiography in this important subset of patients. In a series of 57 women patients, a correct diagnosis was obtained in 85% of women patients and the accuracy was preserved in those with atypical symptoms (84%) and a nondiagnostic stress ECG (82%).

There are several other situations in which exercise echocardiography has proven valuable. Following revascularization, for example, the test is useful to confirm a successful intervention, to detect residual ischemia, and to help plan subsequent management. Two clinical studies have addressed the role of exercise echocardiography following coronary bypass surgery.[38,39] Both have demonstrated the ability of the test to detect and localize nonrevascularized vessels and/or graft disease. The superiority of wall motion analysis over the stress ECG was confirmed in both clinical trials.

A similar approach is possible in patients undergoing angioplasty.[40–42] Prior to the procedure, the stress test can detect and localize ischemia. Afterward, an improvement in rest wall motion can often be demonstrated. The stress echocardiogram can confirm a successful intervention by detecting resolution or a reduction in inducible regional dyssynergy. It may also be possible to detect early restenosis, even when other manifestations of ischemia are absent. Finally, the test can provide a baseline for later comparison, should symptoms recur.

The prognostic value of exercise echocardiography has also been evaluated. Among patients referred for exercise testing because of suspected coronary artery disease, a normal exercise echocardiogram is highly predictive of a good prognosis.[43] If one series of 148 patients followed a mean of 28 ± 9 months after a normal treadmill exercise echocardiogram, the event rate was very low. During follow-up, 4 patients had coronary bypass surgery, 2 patients had MI, and there were no deaths. All 6 events occurred in patients who exercised to a work load <6 METS or achieved $<85\%$ of their age-predicted maximum heart rate.

Valuable prognostic data can also be obtained in patients recovering from MI. Several investigators have studied patients during the convalescent phase following MI and have demonstrated the fundamental relationship between inducible ischemia and outcome (Table V).[44–46] The presence of multiple resting wall motion abnormalities (suggesting multivessel disease) or an induced wall motion abnormality following exercise (suggesting ischemia) identify patients at increased risk for cardiac events over 6–12 months follow-up. Exercise echocardiography would appear ideally suited to provide prognostic information. This likely reflects the fundamental importance of regional LV wall motion as a marker for ischemia.

CONCLUSION

Exercise echocardiography is a technique that can be adapted to a variety of forms of stress testing. It is safe, versatile, cost-effective and clinically useful. It is now established that wall motion analysis increases the accuracy of stress testing to detect coronary artery disease. The increased yield is similar to that provided by nuclear imaging methods, although cost and convenience are clear advantages of echocardiography. It appears likely that the clinical application of this diagnostic test will continue to grow and that it will assume an expanding role in the management of patients with coronary artery disease.

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Dobutamine Stress Echocardiography

David S. Bach, MD, and William F. Armstrong, MD

Two-dimensional echocardiography is a versatile, accurate, and readily available method for the assessment of cardiac anatomy and function, and extensive experience has been gained in the analysis of left ventricular wall motion. Using modern imaging techniques, regional as well as global wall motion analysis can be performed. Echocardiography can be used in conjunction with a protocol for either exercise or pharmacologic cardiovascular stress in order to identify the distribution and severity of coronary artery disease, with the induction of a regional wall motion abnormality being a sign of myocardial ischemia. The use of dobutamine infusion to accomplish stress echocardiography is a safe, accurate, and practical method for the diagnosis of coronary artery disease in patients unable to exercise. In addition to the evaluation of inducible ischemia, preliminary work is being performed with dobutamine stress echocardiography for the assessment of risk and patient prognosis following acute myocardial infarction and as an indication of tissue viability for myocardium that remains dysfunctional at rest following thrombolytic therapy.

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Echocardiography is a versatile, accurate, and readily available method for the evaluation of cardiac anatomy and function. Used in conjunction with exercise or pharmacologic stress protocols, modern 2-dimensional echocardiographic techniques can readily assess regional as well as global left ventricular (LV) function, and provide information regarding the presence, severity, and distribution of coronary artery disease. Infusion of the β-receptor agonist dobutamine to pharmacologically induce cardiovascular "stress" in conjunction with echocardiography is a practical method for the evaluation of cardiac function and the diagnosis of coronary artery disease when the patient is unable to exercise to adequate levels of cardiovascular stress. In addition to the diagnosis of coronary artery disease, preliminary studies suggest that dobutamine stress echocardiography can provide prognostic information following acute myocardial infarction and an indication of tissue viability for myocardium that is dysfunctional at rest following an acute ischemic event or aborted infarction.

WALL MOTION ANALYSIS

LV function can be readily assessed using 2-dimensional echocardiography. Utilizing standard parasternal and apical windows, the left ventricle can be imaged and its walls divided into segments for regional wall motion analysis and assessment of global function. The myocardium is conventionally divided into basal, midcavitary, and apical thirds. Circumferentially, the walls are divided into anterior, lateral, posterior, inferior, inferoseptal, and anteroseptal regions. Functional analysis of regional wall motion is used to identify areas as normal, hypokinetic, akinetic, or dyskinetic. In addition, myocardium that is full-thickness is differentiated from that which is thinned, scarred, and aneurysmal. A wall motion score can be generated by combining the scores of individual regions, providing an indication of overall LV function. In addition, the percentage of normally functioning myocardium can be calculated, providing a quantitative measure of the amount of myocardium that is dysfunctional.

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ECHOCARDIOGRAPHY AND MYOCARDIAL ISCHEMIA

Surface 2-dimensional echocardiography has been used to assess the location and extent of acute myocardial infarction, as well as to identify patients at high risk following myocardial infarction. This has been possible due to the ability of 2-dimensional echocardiography to identify areas of myocardium with abnormal systolic function despite normal wall thickness. The fundamental premise of echocardiographic wall motion analysis is that ischemia or acute infarction results in an abnormal mechanical function of a portion of the left ventricle, which is detected as myocardium that is of normal thickness in diastole but that fails to demonstrate normal systolic thickening. The echocardiographic differentiation of myocardium that is ischemic from that which is recently infarcted is made by monitoring for subsequent functional recovery of that region. Recovery would be suggestive of transient ischemia or stunning, whereas permanent regional dysfunction with subsequent thinning and formation of scar is consistent with myocardial infarction and necrosis.

EXERCISE ECHOCARDIOGRAPHY

The ability to detect regional wall dysfunction has made 2-dimensional echocardiography a useful adjunct to exercise testing for the diagnosis of coronary artery disease. In 1983, Limacher et al[1] published data on the use of echocardiography in conjunction with exercise testing in 73 patients. The sensitivity for detecting coronary artery disease based on an abnormal ejection fraction response or the development of regional wall dyssynergia was 91%, with a specificity of 88%. Berberich et al[2] published data in 1984 with similar sensitivity and specificity results (94% for each parameter) for the detection of coronary artery disease using immediate postexercise echocardiography. Compared with electrocardiographic (ECG) monitoring alone during exercise testing, an improvement in accuracy as well as a reduction in nondiagnostic tests with the use of echocardiography was described in 1 series published by Armstrong et al in 1986[3]. In this series, 35 of 44 patients (80%) with normal resting wall motion on echocardiography and significant coronary artery disease on angiography were identified using exercise echocardiography, compared with only 19 (43%) identified using ECG criteria alone. Among those patients without significant coronary artery disease, 13 of 15 (87%) were correctly diagnosed with exercise echocardiography, compared with only 8 (53%) with ECG, and 18 ambiguous exercise ECG results could be reclassified as diagnostic studies by utilizing echocardiographic wall motion analysis.

The sensitivity and specificity of exercise echocardiography for the diagnosis of coronary artery disease was further evaluated in 123 patients by Armstrong et al in 1987.[4] The sensitivity and specificity for the detection of coronary artery disease were 100% and 72%, respectively, for patients with single-vessel disease, and 97% and 86%, respectively, for patients with multivessel disease. In this series, exercise echocardiography correctly identified 32 of 59 patients (54%) as having multivessel disease. False-negative exercise echocardiograms were obtained in 12 patients (10%), 8 of whom had single-vessel coronary artery disease.

In a series published by Ryan et al[5] in 1988, the sensitivity and specificity of exercise echocardiography among 64 patients with normal resting wall motion were found to be 78% and 100%, respectively. False-negative studies were found only among patients with single-vessel disease, and the sensitivity of exercise echocardiography for the detection of single-vessel disease was found to be superior to that of ECG monitoring alone.

The prognostic value of a normal exercise echocardiogram was described by Sawada et al in 1990.[6] Among 148 patients with normal exercise echocardiograms who were followed for a mean of 28 months, only 6 subsequent cardiac events were noted. All 6 events occurred in patients who achieved <6 METS or <85% of their predicted maximal heart rate with exercise. This confirms that a normal exercise echocardiogram in a patient with good exercise capacity predicts an excellent prognosis with respect to subsequent cardiac events.

NONEXERCISE STRESS ECHOCARDIOGRAPHY

The inability of a patient to exercise and achieve an adequate heart rate and blood pressure response is a major limitation to exercise stress protocols for the diagnosis of coronary artery disease. Physical limitations to exercise may exist secondary to lung disease, peripheral vascular disease, disorders of the central nervous system, or poor general physical conditioning. In order to circumvent the physical limitations of some patients, noninvasive techniques have been developed to provide an assessment for coronary artery disease without the use of exercise.

Several protocols for nonexercise stress testing in conjunction with echocardiographic wall motion analysis have been described. These include the use of static stress modalities such as cold pressor, hand grip, atrial pacing and mental stress, and pharmacologic stress testing including vasodilators such as adenosine and dipyridamole. Inotropic agents such as isoproterenol, dopamine, and dobutamine have also been used for this purpose.

Dipyridamole echocardiography was first described by Picano et al in 1985.[7] Utilizing the maximal coronary vasodilating effect of dipyridamole on the normal coronary vasculature, regions of myocardial flow inhomogeneity can be provoked in the presence of a coronary stenosis. The coronary flow mismatch is sufficient in some cases to induce a wall motion abnormality that can subsequently be detected on echocardiography. Using this as a marker, the sensitivity of dipyridamole echocardiography for the detection of coronary artery disease has been reported to be 53–88%, with greater sensitivity in the presence of multivessel disease and in patients with regional areas of resting myocardial dyssynergia.[8]

DOBUTAMINE STRESS ECHOCARDIOGRAPHY

Dobutamine is a β_1 receptor agonist that exerts positive inotropic activity without significant α or β_2 effects.[9] This results in little effect on peripheral vascular tone and considerably less chronotropic and arrhythmogenic activity than dopamine, norepinephrine, or isoproterenol. It was demonstrated as early as 1976 that dobutamine exerts a differential effect on the perfusion of myocardium supplied by stenotic, as compared with normal, coronary arteries.[10] In patients without coronary artery disease, dobutamine resulted in a greatly increased coronary arterial perfusion, whereas in patients with significant coronary stenoses, dobutamine infusion resulted in an inhomogeneous pattern of coronary perfusion. As was subsequently described by Fung et al,[11] dobutamine is an effective agent for precipitating myocardial dysfunction and is therefore well suited for use in stress protocols that rely on the functional assessment of myocardial performance.

Dobutamine stress echocardiography incorporates the use of 2-dimensional echocardiographic wall motion analysis in the baseline state and during incremental stages of intravenous dobutamine infusion. Specific protocols vary with respect to precise dosage range and the timing of interval stages. One such protocol involves the use of four 3-minute stages of dobutamine infusion, at doses of 5, 10, 20, and 30 μg/kg/min. Heart rate is continuously monitored, and blood pressure and an ECG are recorded at the end of each 3-minute stage. Infusion may be terminated before protocol completion in the event an ischemic response is seen on 2-dimensional echocardiography or in the event of significant ST-segment depression.

Echocardiographic images are obtained at baseline and at the completion of each stage. Using modern electronic equipment, echocardiographic images obtained at baseline, at 5 μg/kg/min, at peak infusion, and at 5 minutes postinfusion are digitized for display in quad-screen format. Wall motion analysis can be performed with side-by-side comparison of each stage in all echocardiographic views.

The normal echocardiographic pattern of LV wall motion during dobutamine infusion is hyperdynamic myocardial contractility, sometimes resulting in near obliteration of the LV cavity during peak infusion. Depicted in Figure 1 is an example of end-diastolic and end-systolic frames from the parasternal long axis view of a normal patient at baseline and during peak dobutamine infusion of 30 μg/kg/min. Myocardial ischemia during dobutamine infusion is visualized echocardiographically as the induction of a regional wall motion abnormality in a coronary arterial perfusion bed. Figure 2 depicts end-diastolic and end-systolic frames from a dobutamine stress echocardiogram in a patient with an occluded left circumflex coronary artery. In this example, the posterior wall becomes akinetic at peak dobutamine infusion.

In 1986, Berthe et al[12] described the use of echocardiographic wall motion analysis during dobutamine infusion to assess for multivessel coronary artery disease in patients following acute myocardial infarction. In this series of 30 patients, dobutamine stress echocardiography correctly identified 11 of 13 patients with multivessel disease, and 15 of 17 patients without coronary disease remote from the area of infarction, yielding a sensitivity and specificity of 85% and 88%, respectively, for identification of patients with multivessel disease. In 1988, Mannering et al[13] studied dobutamine stress echocardiography in 50 patients following myocardial infarction. They described a high level of concordance of results between the dobutamine stress echocardiogram and standard exercise treadmill ECG testing.

Several preliminary studies have been reported describing the use of dobutamine stress echocardiography for the detection of coronary artery disease. Mazeika et al[14] presented a series of 46 patients with suspected coronary artery disease and found a sensitivity of 63% and a specificity of 93%. For patients with 3-vessel disease, the sensitivity in this

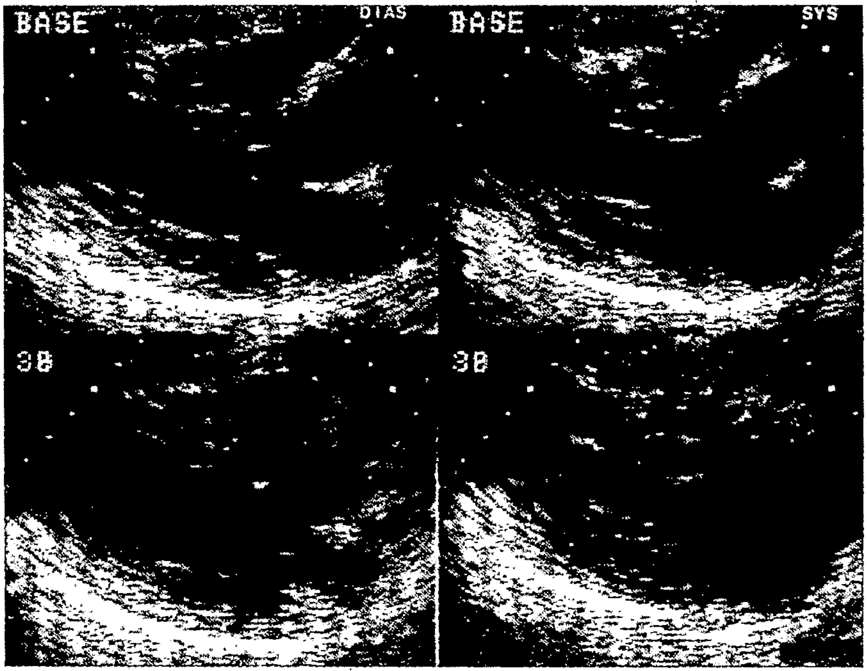

FIGURE 1. Normal dobutamine stress echocardiogram. End-diastolic (*left*) and end-systolic (*right*) frames of parasternal long-axis view of the left ventricle at baseline (*top*) and peak dobutamine infusion of 30 μg/kg/min (*bottom*). The left ventricle demonstrates a normal hyperdynamic "stress" response during dobutamine infusion.

series was 77%. Marcovitz et al[15] described the use of dobutamine stress echocardiography in patients with complex coronary anatomy. In this study of 44 patients, there was an overall sensitivity and specificity for the detection of coronary artery disease of 97% and 45%, respectively. Specificity was adversely affected by the presence of an underlying cardiomyopathy or a resting wall motion abnormality following coronary intervention, with 4 of 6 false-positive dobutamine stress echocardiograms occurring in 1 of these 2 clinical settings.

In 1991, Sawada et al[16] published data from a larger series on dobutamine stress echocardiography for the detection of coronary artery disease. In this study of 103 patients, dobutamine stress echocardiography was used to assess the presence of coronary artery disease both in patients with normal wall motion at rest and for the presence of remote coronary disease in patients with a resting wall motion abnormality. Among 55 patients with normal resting wall motion, dobutamine stress echocardiography correctly identified 31 of 35 patients with coronary artery disease (89% sensitivity) and 17 of 20 patients with no significant coronary artery disease (85% specificity). Specificity was 100% for the 14 patients with multivessel

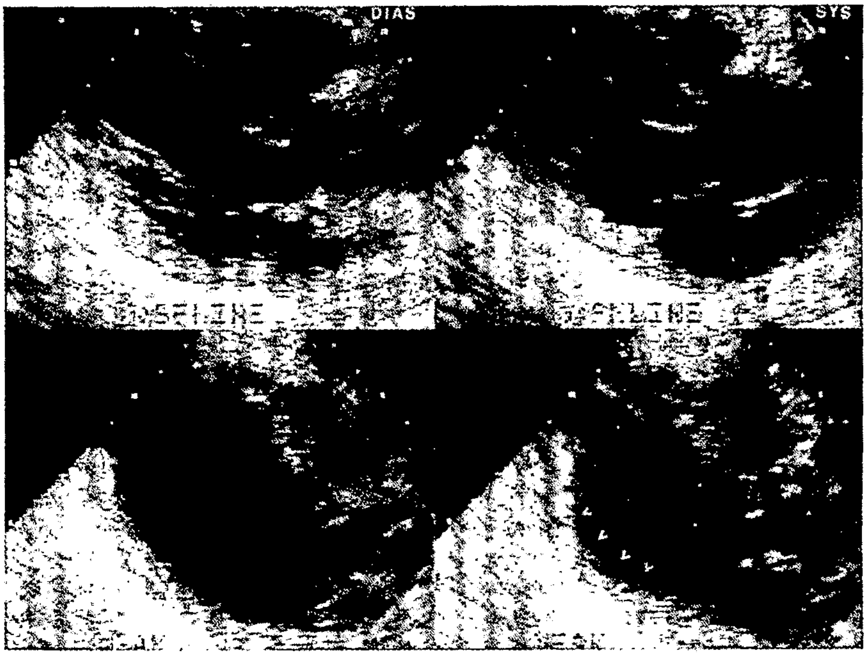

FIGURE 2. Abnormal dobutamine stress echocardiogram. End-diastolic (*left*) and end-systolic (*right*) frames of parasternal long-axis view of the left ventricle at baseline (*top*) and peak dobutamine infusion of 30 μg/kg/min (*bottom*). During peak dobutamine infusion, the posterior wall fails to demonstrate systolic thickening.

disease, and 81% for those with single-vessel disease. Among 48 patients with abnormal LV wall motion at rest, dobutamine stress echocardiography correctly identified 21 of 26 patients with remote coronary artery disease (81% sensitivity), and 13 of 15 patients without distant disease (87% specificity).

Dobutamine stress echocardiography has been used for the assessment of risk following myocardial infarction. In data published in abstract form by Sawada in 1990, an abnormal dobutamine stress echocardiogram was found to be a sensitive predictor of future cardiac events.[17] Among 28 patients followed for the development of unstable angina, congestive heart failure, or death for an average of 6.9 months after myocardial infarction, 8 of 9 morbid events occurred in the 17 patients who had a dobutamine stress echocardiogram positive for a new wall motion abnormality consistent with inducible ischemia. Only 1 event occurred among the 11 patients with a negative dobutamine stress echocardiogram.

ECHOCARDIOGRAPHY AND THROMBOLYSIS

The use of thrombolytic agents has made a marked impact on the subsequent morbidity and mortality following myocardial infarction. The prognosis of the patient and the risk for the development of adverse cardiac events following thrombolytic use during acute myocardial infarction is largely dependent on the size of the infarction and the presence of residually ischemic or jeopardized myocardium. Surface 2-dimensional echocardiography is uniquely suited to evaluate the location and extent of the initial infarction and the degree of functional recovery, as well as assess for the presence of myocardium that remains ischemic versus that which is viable and at risk of reinfarction after thrombolytic therapy.

Echocardiography has been used to describe an improvement in LV wall motion following reperfusion during acute myocardial infarction. In 1988, Presti et al[18] described 16 patients treated with angioplasty during acute anterior wall myocardial infarction. Early treatment was associated with a subsequent improvement in echocardiographic wall motion score. Bourdillon et al[19] described a rapid improvement in LV wall motion following reperfusion, seen as early as 1 day and usually maximal at 3 days following reperfusion therapy for acute myocardial infarction. Broderick et al[20] demonstrated that regional assessment of LV function by 2-dimensional echocardiography after reperfusion was superior to assessment of global function by ejection fraction.

Data from the Thrombolysis in Myocardial Infarction (TIMI) group[21] have reinforced the need to base any interventional procedures following thrombolysis on the presence of recurrent ischemia, as there appears to be no reduction in morbidity or mortality associated with routine catheterization and angioplasty. On the other hand, the noninvasive evaluation of the presence of inducible ischemia following thrombolytic therapy is problematic: Exercise testing without the use of a concomitant imaging modality is confounded by the evolving ST-segment shifts found after acute myocardial infarction, and reports of the use of exercise or dipyridamole "stress" thallium-201 scintigraphy have been associated with poor sensitivity and specificity for both residual stenoses in the infarct-related artery and for the detection of multivessel disease.[22–24]

Dobutamine stress echocardiography in ischemia following thrombolysis: Limited experience has been reported with the use of dobutamine stress echocardiography in the evaluation of patients following thrombolytic therapy for acute myocardial infarction. Although the high sensitivity of dobutamine stress echocardiography for the detection of residual stenoses is retained, there is an apparent reduction in the specificity of the test following acute coronary intervention. Preliminary data from 3 series have been presented on the use of dobutamine stress echocardiography following acute intervention during myocardial infarction. The data previously cited by Marcovitz et al[15] demonstrated a high sensitivity but low specificity for the detection of residual stenoses following coronary intervention. Richards et al[23] reviewed the results of dobutamine stress echocardiography performed 5–7 days after thrombolytic therapy for acute myocardial infarction in 21 patients who had undergone quantitative coronary arteriography. Wall motion abnormalities were induced in 9 of 10 regions with significant stenoses in the territory of the infarct-related artery, and in 4 of 7 regions corresponding to stenoses in the distribution of noninfarct-related arteries. However, in patients without significant residual stenoses, wall motion abnormalities were inducible in 9 of 11 territories corresponding to the infarct-related artery and in 21 of 44 territories distinct from the infarct-related artery. As was previously noted, thallium-201 scintigraphy in these patients had a poor specificity that was nearly identical to that of echocardiography for the detection of significant coronary obstruction.

In another series published in abstract form, Smart et al[25] described the use of dobutamine stress echocardiography in the assessment of multivessel disease or the presence of significant residual stenosis in the infarct-related artery following thrombolytic therapy. A total of 52 patients were studied, 26 of whom had multivessel disease. In this study, the positive and negative predictive values of the dobutamine stress echocardiogram for the presence of multivessel disease were 76% and 74%, respectively. The prediction of residual stenosis in the infarct-related artery was found to be dependent on the presence of viable myocardium in the infarct zone.

DETERMINATION OF VIABILITY

Myocardial stunning following a prolonged ischemic insult is a well-described phenomenon and can be seen after reperfusion therapy.[26] Although the stunned myocardium is viable, there is a persistent wall motion abnormality early after the ischemic event which eventually improves following reperfusion. In addition to assessing for significant residual stenosis in the infarct-related artery and screening for multivessel disease, the management of patients following thrombolytic therapy necessitates establishing the viability of myocardium in regions with persistent wall motion abnormalities.

There is a physiologic basis for the use of dobutamine stress echocardiography for the assessment of tissue viability after an ischemic insult. In 1984, Ellis et al[27] described the use of 2-dimensional echocardiography during a low-dose dobutamine infusion (5–10 μg/kg/min) in an open-chest dog model with myocardium salvaged by reperfusion. In this setting, dobutamine infusion resulted in a significant increase in systolic wall thickening in the reperfusion zone both 1 hour and 24 hours after reperfusion. In another study, isoproterenol infusion was studied using technetium-99m angiography 2 weeks after streptokinase administration for myocardial infarction and the results correlated with vessel patency.[28] Although resting ejection fractions were identical irrespective of vessel patency, there was a significantly greater increase in LV ejection fraction in those patients with a patent infarct-related artery compared with those with persistent occlusion.

These studies provide evidence that, at low doses, inotropic stimulation with β-receptor agonists will result in an increase in LV function in areas of viable myocardium but not in areas of myocardial necrosis. Dobutamine stress echocardiography, with a graduated infusion of the β-receptor agonist dobutamine, is well-suited to provide functional information at incremental levels of inotropic stimulation. The differential response at low doses of dobutamine infusion can be used to distinguish viable (but dysfunctional) from necrotic myocardium and establish tissue viability.

Data supporting the use of dobutamine stress echocardiography for the determination of viability of dysfunctional myocardium following reperfusion in humans come from 2 studies. In 1 study published in 1990, Piérard et al[29] compared metabolic data from positron emission tomography (PET) and functional response data from early dobutamine stress echocardiography with subsequent wall motion recovery in 17 patients treated with thrombolytic therapy for acute myocardial infarction. In the 5 patients in this study with evidence of tissue glucose metabolism and intact myocardial perfusion on PET scanning, an improvement in regional wall thickening on dobutamine stress echocardiography was noted. All 5 had functional recovery on subsequent examination. Of the 6 patients with no evidence of tissue glucose metabolism on PET, none had a significant improvement in wall motion on either early dobutamine stress echocardiography or on later functional evaluation. Analyzing these data for the predictive value of the early dobutamine stress echocardiogram, none of the 7 patients lacking evidence of myocardial viability on early dobutamine stress echocardiography demonstrated any functional recovery on subsequent evaluation. Of the patients with evidence of myocardial viability on early dobutamine stress echocardiography, 7 of 10 (70%) had subsequent functional recovery. Of the 3 patients who did not have later improvement in wall motion, all had early PET analysis positive for glucose metabolism, indicative of tissue viability.

Smart and colleagues[30] published a study in abstract form that similarly addresses functional recovery of myocardium in 33 patients following thrombolytic therapy for acute infarction. In this study, 10 of 15 patients (67%) with improvement of regional wall motion at low doses of dobutamine infusion had subsequent functional recovery. Of 18 patients without evidence of improvement in wall motion on low dose dobutamine infusion, 14 (78%) had no functional improvement on subsequent examination.

CONCLUSION

Dobutamine stress echocardiography is a practical method for the noninvasive assessment for significant coronary artery disease in patients physically unable to exercise. In the absence of a baseline myopathy or prior coronary intervention, it is a sensitive and specific test for the detection of coronary artery disease.

Experience is being gained in using dobutamine stress echocardiography as a tool to establish prognosis after myocardial infarction. In addition, dobutamine stress echocardiography appears to be a promising technique for the assessment of tissue viability for myocardium that remains dysfunctional following reperfusion therapy during acute myocardial infarction.

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Discussion IV: Stress Echocardiography

Dr. Harvey Feigenbaum (Indianapolis, Indiana): At your institutions, do you personally perform stress echocardiography? If so, what type and how frequently?

Dr. Morris Kotler (Philadelphia, Pennsylvania): We started doing exercise treadmill stress echocardiography about a year ago and are now being challenged by our radionuclide imaging colleagues. We do approximately 9–10 radionuclide studies and 1–2 stress echocardiograms a day. However, pharmacologic stress echocardiography is increasing considerably, and we are doing as many as 2–3 of these per day.

Dr. James Weiss (Baltimore, Maryland): Several years ago, we did a large number of stress echocardiographic tests. However, the number of tests has decreased because of the availability of both thallium-201 scans and multiple gated acquisitions (MUGA) blood pool scans, which are much less labor intensive for the echocardiography laboratory. More recently, we have been doing occasional exercise stress echocardiograms as well as pharmacologic stress echocardiograms with both dipyridamole and dobutamine. I believe there will be a resurgence of stress echocardiography; labor intensiveness was the major factor that caused the decrease.

Dr. Kent Richards (Albuquerque, New Mexico): We do stress echocardiography at the Veterans Administration Hospital with both exercise stress (with an upright bicycle) and dobutamine. We do about 2 tests per day, and they are frequently done in a research mode where we compare the dobutamine and standing stress echo tests.

Dr. Feigenbaum: Dr. Weiss, in regard to the labor-intensiveness issue, has that been resolved or is it still a problem to overcome?

Dr. Weiss: It is still a problem to overcome. Other problems we encounter are space, a dedicated machine (which in our institution is an upright bicycle), and a technician for the duration of the test. We must also be able to overcome these hurdles in the presence of very easily available nuclear studies.

Dr. Miguel Quiñones (Houston, Texas): When we started performing the dobutamine stress tests, I discovered that I had to go through a learning curve. Part of the problem was that the ventricular displacement gets so small that any wall motion abnormality is difficult to see. In the panel's opinion, is that simply a personal, or is it a general, experience and are there ways to prevent the ventricular motion from becoming so small?

Dr. William F. Armstrong (Ann Arbor, Michigan): There are some subtle differences in how the heart appears during dobutamine stress compared with exercise stress, and you are not the first person to mention this. A number of these patients do get hyperdynamic small cavity obliteration. Finding a wall motion abnormality in 2 of 16 segments, while another 14 are trying to obliterate, can be a serious problem. We have seen this effect in patients who were subsequently proven to have a false-negative result.

Dr. Thomas Ryan (Indianapolis, Indiana): As part of the prerenal transplant protocol at our institution, we have to get a dobutamine stress echocardiogram, and so we have the opportunity to study many dialysis patients. Whenever we do a study right after dialysis, where their preload activity is relatively low, we see hyperdynamic small-cavity obliteration. This is probably related to preload, and I think trying to avoid hypovolemia and preload reduction prior to the study may prevent part of the effect—but it is clearly related to the problem.

Dr. Christopher Appleton (Tucson, Arizona): I wonder if the difference between the pharmacologic stress and exercise stress tests does not also explain the difference in hypotension. When we put patients on the treadmill test, not very many become hypotensive.

Dr. Armstrong: They are not hypotensive compared to the rest; they are hypotensive compared to the blood pressure curve.

Participant: To ask a related question, what is your opinion about the lack of electrocardiographic (ECG) changes? I find it surprising.

Dr. Armstrong: I believe that that has been everyone's experience with dobutamine.

Participant: Do you think exercise ECG is comparable with the treadmill?

Dr. Armstrong: No, it is well below the accuracy one gets with treadmill or bicycle.

Dr. Ryan: The difference in accuracy between exercise and pharmacologic stress tests may stem from 2 causes. One is that it is very difficult to interpret ST-segment changes with dobutamine because there is no apparent ST segment in an echocardiogram. The second reason is that dobutamine echocardiography uses wall motion as an end point and, on noticing a wall motion abnormality, you can in most circumstances stop the test before the more classic manifestations of ischemia, such as ST-segment depression, become apparent. I would argue that wall motion is an earlier manifestation of ischemia than ECG changes.

Dr. Weiss: I believe that wall motion abnormality is probably an earlier event than ST-segment changes in manifest ischemia. Dr. Armstrong, have you made a direct comparison in your own patients between pharmacologic studies and treadmill tests? The reason I ask is partially from an economic standpoint. For this technique to become more universally acceptable, we are going to have to prove it, not only as comparably useful, but as being more useful and accurate than the standard treadmill test.

Dr. Armstrong: We have not compared the prognostic value of standard treadmill testing versus pharmacologic stress echocardiography. A study published several years ago did review that, and the value of the echocardiogram was found to be statistically superior to that of the ECG plus symptoms during a functional treadmill test.

Dr. Feigenbaum: Your comment is important. Dr. Ryan did one of our first prognostic studies of postmyocardial infarction, and one of the most significant items from his data is the fact that there were only 40 patients. When I presented that information to groups, many of whom were nuclear cardiologists, they were skeptical because of the small patient sample size—in other words, they considered this a preliminary study. But if a technique works well, it will work well almost every time, and from a prognostic point of view, this is what we have been finding with every wall motion study we have done, whether with dobutamine or with exercise.

Dr. Ryan: I have a slightly different approach to this general issue. A question I am asked frequently is, "If dobutamine is so good, should we be doing dobutamine instead of exercise?" The issue concerning postinfarction risk stratification is another way to say that with exercise testing we are looking for multivessel disease and inducible ischemia. There is no doubt that an ECG provides this information. Wall motion gives similar information, but dobutamine testing not only provides information about multivessel disease and inducible ischemia, it also potentially provides information about the viability of the infarct zone. If you are considering a cost-effective postinfarct risk stratification study with the maximum amount of prognostic information, one key issue is the question of viability that dobutamine provides and that exercise does not.

Dr. Weiss Viability might cut both ways. It is possible to pick up a viable segment that could be a favorable prognostic sign, but it could also be potentially unfavorable in that it might undergo infarction and cause trouble.

Dr. Ryan: That is possible, but I would argue that my data do not support this.

Dr. Nathaniel Reichek (Philadelphia, Pennsylvania): In using prolonged dobutamine infusion for our magnetic resonance work, we have observed that you really do not achieve steady-state periods. Has anyone performed dobutamine stress echocardiography with longer infusion periods?

Participant: We have been doing 5-minute infusion periods for that very reason, because dobutamine is unlike an exercise treadmill test, which achieves maximum heart rate and blood pressure after 2 minutes. Because, this is not true with dobutamine, we have been going to 3.5–4-minute infusion periods before we start imaging.

Participant: Pharmacologists will say that you have not reached steady state in ≤ 3 minutes, so some practitioners are doing longer infusions. From a practical standpoint, it becomes important to perform the tests for patients within a reasonable amount of time.

Dr. Benjamin Byrd (Nashville, Tennessee): Especially with protracted infusions, the time commitment for these tests can be a real problem.

Dr. Feigenbaum: That is right. The practical aspects of performing these tests are extremely important. One of the reasons our stress echocardiography program has been successful is due to patient acceptance as well as referral physician acceptance. We have many outpatients who appreciate the fact that they do not have to come back for reperfusion. Currently, the patient will be there for <1 hour, and results are almost immediately available. The test should not be longer than 45 minutes to 1 hour, or it will not prove practical.

Cost-effectiveness is another practical consideration. The costs in time, personnel, equipment, depreciation, and disposables probably reflect the local economy, regardless of the region. In our institution, a stress echocardiogram costs about $500, and a stress thallium-201 scintigraphy test is $1,200. That is a $>2:1$ ratio.

Participant: What do treadmill tests cost?

Dr. Feigenbaum: I assume that it would be approximately half of the echocardiogram. That is what it is at our institution.

Dr. Weiss: That's all the more reason for proving the hypothesis that stress echocardiography is not just as good as, but better than, other testing modalities.

Dr. Feigenbaum: Regarding your comment, Dr. Weiss, when we evaluate any imaging stress test versus ECG in practicing cardiology today, we need to know more than just whether or not a patient has ischemia. We know that the majority of patients that we stress have coronary artery disease. We need more information about their management. In that regard, the regional wall motion information that echocardiography provides is valuable.

We must emphasize the advantages of stress echocardiography because we are in a competitive situation. Nonmedical personnel are making important decisions today regarding instrumentation. Unfortunately the data they rely on are not necessarily accurate and could possibly lead to poor choices. In addition, costs for equipment or procedures must be somehow related to costs for similar equipment or services, and not arbitrarily set, which happens frequently. As an example, our administration required that I list our original start-up costs, including equipment costs, depreciation costs, technicians needed, and staff salaries. They used this information to establish an overall cost.

Participant: These are pertinent comments, but since I was chairman of a study that evaluated angioplasty and single-vessel disease, I have been concerned with the technical aspects of the current methodology. What impresses me is that we always assess against the coronary arteriogram. In our study with approximately 600 patients, using either thallium scintigraphy or the exercise ECG, we had 75 patients with single-vessel disease for whom we could not get a positive test in order to randomize the procedure. On evaluation, however, 2 population groups emerged. One group was recently postinfarction; the other group of patients was subdivided into 2 groups, in one of whom 70% were seen to have lesions versus the rest, in whom 90% had lesions.

The point I am trying to make is that a coronary arteriogram done at time "x" may not be the appropriate standard for an exercise test done at time "y," and perhaps these stress test event rates provide more meaningful interpretations of outcome. We should not expect perfect tests. The coronary arteriogram is a static anatomic standard for physiologic events, and I believe these dynamic stress tests may have much more meaning in terms of what is happening than a static image on a coronary arteriogram.

Dr. Feigenbaum: You are absolutely right. If we examine the Coronary Artery Survival Study (CASS) data, coronary angiography is a relatively poor prognostic indicator when compared with straight ventricular function. Regarding prognosis, the CASS data evaluated coronary anatomy, global ventricular function, and regional ventricular function. Of the 3, regional ventricular function is clearly the best prognostic indicator. Coronary anatomy is an unsatisfactory "gold standard," because it overlooks significant disease and, unless you closely examine the morphology of the lesions, you cannot predict anything except percent stenosis.

Dr. Ryan: Dr. Armstrong, what about ejection fraction (EF) and heart rate?

Dr. Armstrong: I am not an advocate of calculating the EF in all patients. However, in our hypotension study we calculated the EF at each stage, and we discovered that the decrease in EF seen in several patients did not detect regional abnormality.

Dr. Feigenbaum: From an echocardiography point of view, calculating the EF is not one of our strong suits because it is manpower intensive. The regional wall data that we are using works reasonably well, and I am sure we will improve in this area. While we are looking for better quantitation, manually tracing this factor is a time-consuming approach.

Dr. Armstrong: Calculating the EF is more or less required at our institution and it takes me about 90 seconds for both the rest and stress data. A good off-line system will print out everything, including the center line, on a laser printer.

Dr. Feigenbaum: We will start the second panel with the same question I asked the first; are you doing routine echocardiography studies in your institution? If so, what kind? If not, why not?

Dr. Quiñones: We began doing exercise echocardiograms in 1981 with the post-treadmill technique, and we have continued doing treadmill exercise 2-dimensional echocardiography.

In the near future, one of the decisions we as echocardiographers have to make is whether we want stress echocardiography to become the inexpensive screener that supplants routine stress ECG, or if stress echocardiography can reach to the level of being the more expensive, but more definitive, stress technique. In the second case, which I favor, we compete with the nuclear imaging laboratories. To remain in the middle, undefined between being either an inexpensive screener or a definitive testing modality, is not a wise choice if we are going to make a serious impact in the area of stress testing.

I also think that we have a perception problem, and we must face certain challenges if we are to succeed in advancing our technique. The issues involve accuracy, reproducibility, and prognostic value. Regarding accuracy, single photon emission computed tomography (SPECT) is perceived as being superior because it is more quantitative and yields better results. Another challenge is reproducibility and addressing the question, Can we really get the same results? We need to develop some type of quantitative parameters that we can present more effectively than a wall motion score. Finally, there is the importance of prognostic value and the emphasis on multicenter studies with clinically large numbers. In sum, we need to take the prognostic data out into the community to overcome any negative perceptions among nonechocardiographers.

Dr. Randolph Martin (Atlanta, Georgia): We have done several vascular studies at Emory and have recently begun dobutamine stress echocardiography. We are doing about 3–4 studies per day and are limited primarily by manpower.

First, I agree with the points made by Dr. Quiñones. If you examine the literature, it reports almost exclusively thallium-201 scan results, so the perception of our colleagues as well as the noncardiologists is that thallium-201 scintigraphy is the noninvasive procedure of choice.

Second, we are definitely in a competitive relationship. Basically, we are competing with another modality to be *the* noninvasive diagnostic procedure. It is a plus if it provides more accurate information and I cannot overemphasize enough what Dr. Quiñones said about the importance of prognostic information. Although exercise or pharmacologic stress echocardiography has a high degree of accuracy and can offer prognostic information, it is not currently perceived as a first-line methodology. For the reasons that Dr. Quiñones mentioned, I believe we have to pursue those challenges actively. Until we can get reproducible, graphically good information from a stress test, I think stress echocardiography will be viewed as a lesser technology.

Dr. Michael Crawford (Albuquerque, New Mexico): We are performing a combination of both exercise and dobutamine stress echocardiography and probably do about 3–5 per day. We have both bicycle and treadmill available. I use the bicycle exclusively for research because it is easier to quantitate exercise workloads on it, but for clinical purposes we use the treadmill. We have heard some of the pros and cons of the 2 test types from Dr. Ryan, but I would like to mention 2 other issues. First, average patients can achieve a higher workload on a treadmill test than they can on a bicycle. There is more stress on the myocardium with the treadmill. Second, in the average laboratory I think image quality is better immediately postexercise when lying down after the treadmill test than when upright or even supine while pedaling the bicycle. It is challenging to get an image during peak exercise on a bicycle; it is possible, but I believe we get better image quality post-treadmill.

Dr. Quiñones: For those of you who have used the exercise bicycle, is it easier supine or upright? Does it make any difference? Are both equally difficult?

Dr. Crawford: I think it is a little easier to get a good image supine, if you can get patients to pedal while they are lying on their left side. That's the challenge. If they pedal flat on their back, then it is actually harder to get a supine image, but it is possible.

Dr. Feigenbaum: We do supine imaging at rest. We get 4 views, just as with a treadmill, because we actually did the treadmill first. Our treadmill is followed by 4 views lying down. We do the same thing with the bicycle, but in between we get another upright, apical 2- and 4-chamber view. We get 4 views lying down for rest, then with the bicycle we get the apical 2- and 4-chamber views again, because the 2 resting views are not exact. Then we do the bicycle again and get the apical views at peak exercise stress. Finally, the patients lie down and we get 4 views again. It is a hybrid test.

Dr. John Gottdiener (Washington, D.C.): We have been doing echocardiography at Georgetown University as part of a research protocol where we not only perform exercise stress, but also mental stress testing. This is not because mental stress is an effective producer of ischemia, but because we are examining behavioral predictors of ischemia. What has become apparent from these studies where we do continuous monitoring during upright bicycle exercise is that this is a very difficult technique to interpret. There is a tendency to assume that the thallium-201 and MUGA images are obtained with high-tech information, whereas we are using what is seen as low-tech information.

Second, our images need quantification, and the learning curve takes months.

Another issue is the price of the equipment. A digital image display acquisition analysis system can cost upward of $50,000, and basically the result is $10,000 worth of hardware that may be used only occasionally in a busy echo laboratory.

Dr. Crawford: Currently, we have a number of modalities that we can compare with stress echocardiography. We have echocardiographic imaging that informs us about coronary anatomy, detects ischemia, and compares this with an arteriography study as our "gold standard." We also have tests that tell us about perfusion. Is there independent information at each level regarding anatomy, perfusion, and ischemia that will help us with either prognosis or decision-making in our patients? I would also like to ask the panel, what is the unique advantage of stress echocardiography in defining the course of action for our patients and how does it differ from the other modalities that provide information about coronary anatomy versus perfusion information? How can we capitalize on these advantages to market our product; stress echocardiography?

Dr. Quiñones: Those are excellent questions. The answers depend on what we ourselves think of stress echocardiography and, perhaps more importantly, what is the community's perception. Again, I think thallium scintigraphy has done very well regarding public relations, and in the same way that there is a knee-jerk response in *ordering* a thallium scan, there is a knee-jerk response in acting on the thallium scan. Nuclear practitioners have successfully established an answer to your question, but we have not. I believe that among ourselves we know the answer to what echocardiography will do. When you see real wall motion and ischemia developing in the echocardiogram, I think we certainly can establish algorithms that will have clinical impact on patient care.

Dr. Armstrong: With respect to everyone's comments, I wish to challenge the marketing issue. We started at zero stress echocardiograms per year and now we have increased to about 1,000/year. That is parallel to the growth in the laboratory in general. What contributed to effective marketing is the versatility of the examination and the speed with which we can provide results. We work under very restrictive rules and regulations regarding reimbursement. The functional significance of the lesion must be demonstrated before we can dilate and receive reimbursement. When patients are brought in from 200 miles away for a diagnostic catheterization, I can provide them with a dobutamine stress echocardiogram at 8 A.M. with results at 9:15 A.M., and then they can go to the catheterization laboratory. Nuclear medicine cannot operate so efficiently. Stress echocardiography can provide a level of versatility that gives resting ventricular function, frequently avoids an angiogram, answers all the valvular and other incidental questions, and settles the ischemia issue by 9:15 in the morning—when the patient can then proceed to the catheterization laboratory. The versatility and speed with which we can operate is a tremendous marketing advantage.

Dr. Crawford: We can best position ourselves for marketing stress echocardiography if it provides unique information that cannot be provided by any other test. However, if it is only a matter of versatility, expense, or quickness, we are in an inferior position.

Dr. Armstrong: Not at all. Stress echocardiography is not any more accurate than nuclear medicine. They have accurate tests, but from a functional standpoint, nuclear studies are cumbersome and unidimensional. I think we need to capitalize on our versatility and convenience.

Participant: Because thallium scintigraphy works very well, people use it. In order to market stress echocardiography, we have to find a niche where this technique actually benefits patients more than the thallium scans do. We are saying now that we have to compete with them, but we are not going to eliminate them from the market. We have to find the specific area where we can outperform thallium testing. One area to improve is the detection of single-vessel disease. We know we miss single-vessel disease and that the thallium experts can detect it better than we can. That is very unsatisfactory.

Dr. Steven Nissen (Lexington, Kentucky): Is it important to detect single-vessel disease?

Participant: Yes, absolutely, because I do not treat any asymptomatic patients. I test patients who come in with chest pain and check to see if they have coronary disease, especially single-vessel. If I miss it and thallium scintigraphy detects it, that is our problem.

Dr. Sanjiv Kaul (Charlottesville, Virginia): As the new cardiologist in the group, I would like to make a few comments and suggest some possibilities where exercise echocardiography might offer additional information. For example, we talk about diagnosis and detection of coronary disease, but that is not really the issue. What we need to know is, How much disease does the patient have? Do I have to intervene or can I send the patient home? Therefore, prognosis becomes extremely important. Two areas to look for are prognosis in postmyocardial infarction and also in patients with garden-variety coronary artery disease. Second, what are the events? For example, is infarction being predicted by exercise echocardiography. Also, we have discussed only patients who did not receive thrombolytic therapy, and today that is a minority. This is also an area where exercise echocardiography may be advantageous because thallium scintigraphy is not as effective in the postmyocardial infarction arena. In the post-thrombolytic arena we are not as effective at detecting remote ischemia, although we do surpass exercise ECG.

These are important questions. Another potential is the additive effect, and I think this is what Dr. Weiss was referring to. The question becomes, how much did the echocardiogram add to the weight of other test results? The additive effect is an advantage that is marketable. It is not only a unique effect, but an additive effect as well. In my opinion these are areas where exercise echocardiography may have a greater role to play.

Participant: In reality, the greatest likelihood for stress echocardiography to prevail, given the direction of U.S. medicine in the past few years, is that a strong case can be made that stress echocardiography is equivalent to thallium scintigraphy but less expensive, even by 30%. Enormous economic pressure will be applied, and the opportunity is there.

Dr. Edward Geiser (Gainesville, Florida): We have been discussing competition, marketing, and our niche relative to the positioning of thallium scintigraphy. I think it is important to evaluate what happens without the marketing consideration. I do not argue that exercise echocardiography can be done, or that the data are as accurate as the thallium data. It has been our experience that wall motion analysis is probably one of the most difficult diagnostic aspects of echocardiography.

When the medical community is in an environment where the laboratory is not marketing and marketing is not promoting, then there will be no issue at all. When someone says they can provide a unique service because they were able to organize information into a framework that meets the demands for the environment, then they speak for themselves. However, I do not think that trying to market echocardiography to a community with a unique application is really providing a criticial medical service.

Dr. Martin: The fact is that we are no longer in an era where there are no outside limitations on patient management. We have to show accuracy, cost-effectiveness, and a recognition that we are not the only ones making the decisions. In the future the marketing aspect will at least partially drive the system, and we must be prepared to prove the cost-effectiveness of our technology in the management of patients.

Dr. Skorton: A point I want to make is that nuclear and magnetic resonance imaging may actually teach us more physiology; in other words, they could prove to be a benefit to those of us in echocardiography. Massachusetts General Hospital has a machine that does 20 scans/sec. There is no question that we will be able to determine function, perfusion, and similar values but it will not compete with echocardiography. What will result from these magnetic resonance studies and from the PET units is that we are going to learn, for example, that phosphorus-31 levels can decrease and that patients improve. This may seem to be paradoxical.

The method of making echocardiography successful is not to oversell what it is; keep it simple and straightforward. We should provide global functional information because not all of the studies of radionuclide blood pool scanning are shown to be a reasonable way to detect coronary disease. We need to prognosticate and combine global and regional functional information. We also must address the 3 issues of cost-effectiveness, making sure that we are competitively priced, keeping it simple and straightforward diagnostically, and not going too far in saying what the technique can do. There are no exact predictions.

Dr. Crawford: To consider this issue in a cost/marketing mode, I found that I could position stress echocardiography to make it popular. I asked clinicians, do you want anatomic information about this heart? Do you need information on left ventricular hypertrophy? Do you need to know how the valves are working? In many patients, clinicians will order a stress thallium scan and also an echocardiogram. I said, if you are planning to get an echocardiogram anyway, we can do a stress echocardiogram and give you the same information you would get with a thallium scan. With one test we will provide all the information at a reduced cost. The result was that it was both cost-effective and the volume increased 60% in 1 year.

Dr. Feigenbaum: I've always defined myself as a clinical cardiologist. I believe that ultrasound is an extension of the physical examination. As a clinician who uses ultrasound as a "true stethoscope," I believe it should be developed to its fullest potential for the evaluation of coronary artery disease. Our own stress echocardiography program has gone very well because the technology really works. However, on a national basis, as long as there are experts in echocardiography who still express serious doubts, we will have obstacles to overcome. It is our intention to resolve those doubts, which should not be a problem because we have the data to support our technique.

Dr. Martin: I think all of us here value echocardiography and recognize it as a highly effective diagnostic tool in current and future patient management.

Dr. Gottdiener: Echocardiography has a unique problem in that it is operator-interaction dependent. There is no other cardiology imaging technique in which both the process and the information are so critically dependent on the second-by-second, beat-by-beat recognition by the individual performing the study.

Dr. Feigenbaum: I work in the catheterization laboratory, which is still considered to be the "gold standard." I hear that comment all the time. I will not ever minimize our technical difficulties, but we certainly do not have any more than the catheterization laboratory, and I know there are technical difficulties with nuclear studies. One of our problems is that echocardiography does not provide color images, and we have to make interpretations from suboptimal situations. However, as far as clinical information is concerned, it is extremely valuable.

Dr. Skorton: At this time, it is not true that echocardiography is significantly more operator-dependent. My impression of nuclear imaging is that it is even more operator-dependent. SPECT is dependent on the image-processing algorithm, as well as on various technician judgments. As for magnetic resonance imaging, from the time the pulse sequence is chosen to displaying the image in the window, the result is also operator-dependent.

Although echocardiography is still operator-dependent to an extent, the gap is narrowing, because the other technologies are developing more options and are therefore becoming more operator-dependent.

Dr. Armstrong: I agree about magnetic resonance imaging. One of the reasons magnetic resonance determinations are often delegated to echocardiographers is because we have the expertise to deal with some of the subjective complexities.

Dr. Bijoy Khandheria (Rochester, Minnesota): Nuclear medicine is also advancing. There are developments with a new agent, technetium-99m, for gated thallium-201 images with wall motion.

Dr. Feigenbaum: However, if you look at the inherent resolution, we should still be quite competitive.

Quantitative Ultrasonic Imaging: Tissue Characterization and Instantaneous Quantification of Cardiac Function

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Quantitative myocardial tissue characterization is being developed to complement and expand conventional echocardiography by delineating the physical state of myocardium under diverse pathophysiologic conditions. Real-time quantitative integrated backscatter imaging has already been applied to patients with ischemic heart disease, hypertrophic cardiomyopathy, and cardiac allograft rejection in clinical investigations performed in the United States, Europe, and Japan. A recently introduced modification of imaging processing algorithms employed for characterization of tissue facilitates automatic detection of endocardial–blood interfaces and on-line quantification of ventricular size and function. Further progress and anticipated developments in quantitative ultrasonic imaging will undoubtedly augment the clinical applications of tissue characterizations based on myocardial integrated backscatter for improved diagnosis, elucidation of pathophysiology, and assessment of cardiac function.

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Tomographic imaging with 2-dimensional echocardiography was developed in part to improve measurements of cardiac chamber dimensions and function.[1,2] Implementation of digital technology facilitated off-line analysis of the 2-dimensional images obtained and estimation of ventricular size and function. Several approaches have been developed to permit automated detection of the endocardial–blood boundaries of the left ventricle and to provide more rapid assessment of regional function.[3–7] However, despite their merit, most still require off-line computer processing. Accordingly, despite the development of recommendations by the American Society of Echocardiography,[8] routine quantification of ventricular function has not been adopted for general use, in part because of the time-consuming nature of off-line analysis.

While 2-dimensional echocardiography was evolving, a parallel development was emerging for quantitative acoustic characterization of the structure of the myocardium by measurement of integrated backscatter. This approach ultimately gave rise to an imaging modality suitable for clinical applications.[9–12] The procedure that was developed is fundamentally different from conventional echocardiography in that a quantitative measurement (in decibels, dB) of the power along each radiofrequency line in the scanning field of view is made before the resulting quantitative information obtained is relayed to the scan converter for construction of the real-time image. Recently, the quantitative image-processing approach has been coupled with 2-dimensional imaging utilizing automated edge detection. The convergence of 2-dimensional echocardiography and quantitative backscatter imaging has improved previous approaches[13] and permitted on-line quantification of ventricular function.[14–16] This brief review summarizes the results obtained in laboratory studies (on which the clinical progress was predicated), results of quanti-

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tative myocardial tissue characterization in hearts of laboratory animals, and clinical validation and applications of automatic boundary detection for on-line quantification of ventricular function by quantitative integrated backscatter imaging.

PRINCIPLES OF TISSUE CHARACTERIZATION WITH RADIOFREQUENCY SIGNALS FROM MYOCARDIUM

Specular versus intramyocardial echoes: The fundamental difference between quantitative myocardial tissue characterization and conventional echocardiography relates to the different acoustic interfaces interrogated ultrasonically by each modality. In conventional imaging the specular reflections (e.g., interfaces between endocardium and blood) are the reflections used for delineation of ventricular walls and valve surfaces. Such reflections occur when the incident ultrasonic wavelength is much smaller than the dimensions of the boundary. In tissue characterization with backscatter imaging, even though specular reflections are well outlined, images are constructed primarily from echoes derived from very small intramyocardial targets (i.e., within the endocardial/epicardial borders). Thus, in characterization of intramural tissue, the wavelength is larger than the dimensions of the interfaces or boundaries of specific structural components within the myocardial tissue. Instead of being reflected, as is the case with specular echoes, the incident waveforms are scattered. One component is scattered 180° opposite to the ultrasound emanating from the transmitting transducer, and this is defined as backscatter.

Backscattered radiofrequency waveforms result from interactions between the transmitted ultrasound and structural inhomogeneities in the tissue. Thus, the extent or amount of backscatter from a segment of tissue, expressed in decibels and called integrated backscatter, is a descriptive parameter sensitive to tissue structure and therefore useful for characterization of properties of tissue in quantitative terms.

INTEGRATED BACKSCATTER IMAGING

Although ultrasonic waveforms can be analyzed in diverse ways, the approach that our group at Washington University has taken for real-time imaging entails time-domain analysis[17] of the radiofrequency signals backscattered from the myocardial segment of interest, with squaring and summation of the signal. This method of estimation of the backscatter, as opposed to the more accurate but time-consuming frequency-domain analysis, employs a 3 μsec integration time, resulting in analysis of multiple (typically, 100) individual points along each radiofrequency line. The average power obtained from each radiofrequency line is compared with a reference power spectrum within the imaging system to express integrated backscatter in decibels along each line (Figure 1). The information obtained is relayed to the scan converter and employed to construct a real-time image.[18] With this approach, no postprocessing of the acoustic data is needed for delineation of the tissue, and the real-time image is fully quantitated in decibels (Figure 2). Regional myocardial integrated backscatter can be obtained by placement of regions of interest within the mural myocardium, thereby avoiding the bright specular echoes of the endocardial–blood interfaces with guidance by the real-time 2-dimensional image or by an M-mode signal directed to the segment of interest.

In earlier studies performed in laboratory ani-

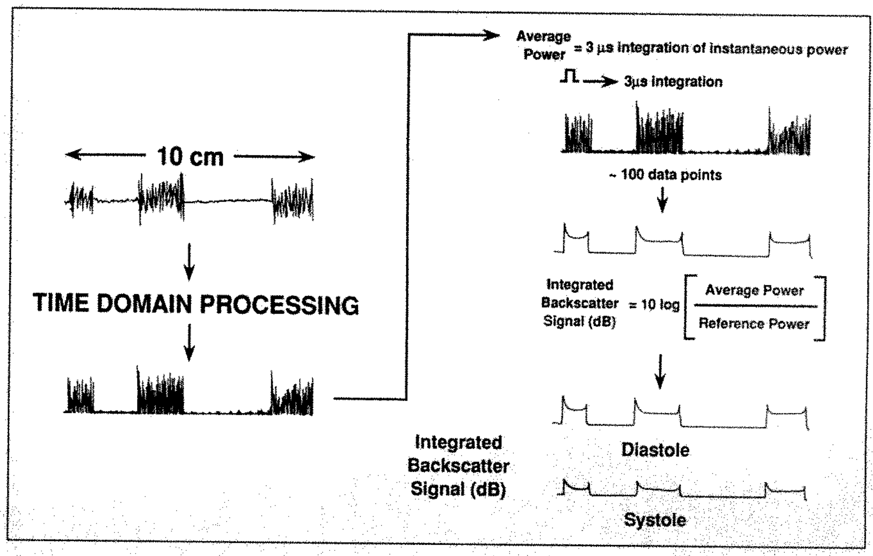
10 cm
TIME DOMAIN PROCESSING
Average Power = 3 μs integration of instantaneous power
3μs integration
~ 100 data points
Integrated Backscatter Signal (dB) = 10 log [Average Power / Reference Power]
Integrated Backscatter Signal (dB)
Diastole
Systole

FIGURE 1. Schematic representation of the pathway of analysis of a single radiofrequency signal (one A-line; parasternal long-axis view, showing right ventricular, septal, and posterior wall data) after backscatter from myocardium. After time-domain processing, integration is carried out, and the signal strength is referenced to an internal standard to yield power in decibels (dB). The power in diastole is higher than in systole in all intramyocardial regions.

TABLE I Investigators Who Have Used the Cyclic Variation of Myocardial Backscatter

Institution	City	Year
Washington University	St. Louis, MO	1983
University of Iowa	Iowa City	1984
Medical College–Wisconsin	Milwaukee, WI	1986
Dartmouth–Hitchcock	Hanover, NH	1986
University of Munich	Munich	1987
Cedars-Sinai	Los Angeles	1988
Thoraxcenter–Erasmus	Rotterdam	1988
Stanford	Stanford, CA	1989
University of Rochester	Rochester, NY	1989
Osaka University	Osaka, Japan	1990
Albert Einstein	New York, NY	1991

mals we used measurements analyzed in the frequency domain[19] and found that integrated backscatter of normal myocardium exhibits cardiac cycle-dependent variation with higher values (higher intensity) in late diastole and lower values in systole (Figure 3). This pattern of diastolic-to-systolic variation could be recognized with the time-domain measurement imaging system developed for backscatter imaging in patients. Cyclic variation of backscatter from normal myocardium has now been widely appreciated (Table I) and represents a useful parameter that can be obtained in vivo with the commercially developed system. Its presence permits assessment of viability of myocardial tissue in hearts of laboratory animals and patients.[20,21]

Additional measurement of tissue characteristics are required to delineate specific structural and functional features of myocardium and for accurate assessments in serial studies in the same patient, as well as for between-patient comparisons of absolute amounts of myocardial integrated backscatter. Preliminary observations by Masuyama et al,[22] results by Rhyne et al,[23] and those of Landini and coworkers[24] suggest that absolute quantitation of the returned signals is feasible in backscatter imaging systems developed for clinical use. Furthermore, novel indexes of tissue characterization of hearts of experimental animals such as frequency-dependence of backscatter can differentiate normal from recently ischemic and from irreversibly injured myocardium in the same heart in vivo. The measurements obtained depend on the dimensions of the dominant scatterer within tissue and are promising for differentiation of ischemic-yet-viable from necrotic myocardium that has undergone infarction despite equally asynergic segmental wall motion in both.[25]

Backscatter measurements should be applicable for interrogation of myocardium from different echocardiographic projections, including apical 4- and apical 2-chamber views in addition to the parasternal projection generally employed to date. Such projections are needed for optimal evaluation of myocardium in segments such as the apex, which is frequently involved when ischemic heart disease is present.

RESULTS IN STUDIES OF ANIMALS UNDERLYING CLINICAL DEVELOPMENT OF BACKSCATTER IMAGING

Utilizing the measurement of integrated backscatter of myocardium, we found that the content of collagen in tissue associated with previous infarc-

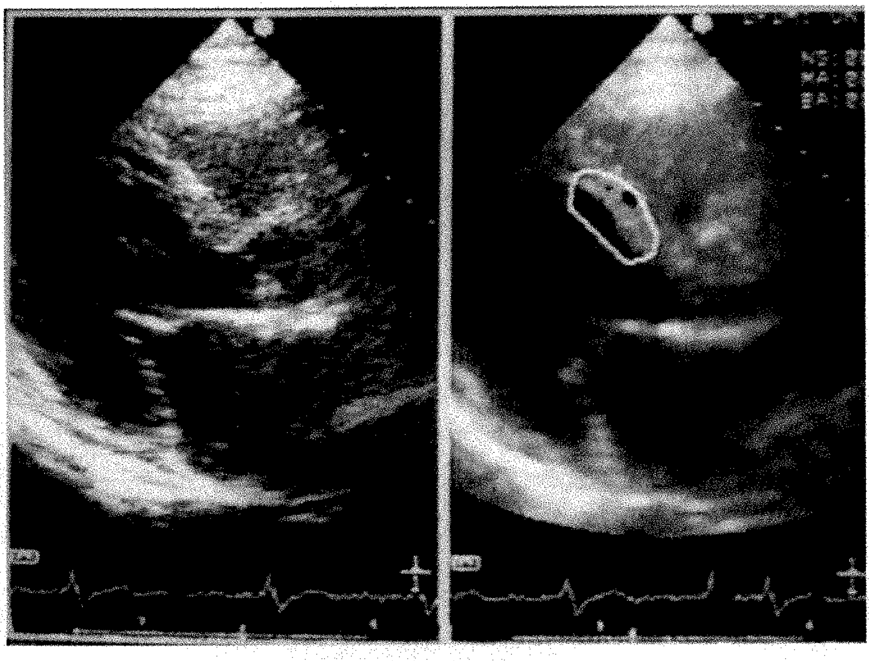

FIGURE 2. Freeze-frame parasternal long-axis conventional (*left*) and 2-dimensional ultrasonic integrated backscatter images (*right*) obtained in a patient with posterior wall infarction. The region of interest has been placed in the normal midseptum encompassing both tissue and blood. The threshold level settings (*dark areas*) eliminate backscatter data from the blood pool and a relatively bright region within the tissue.

tion is a major determinant of the magnitude of backscatter.[26] Measurements performed in open-chest dogs with acute infarction demonstrated increased levels of backscatter as early as 1 hour after coronary occlusion.[27] In addition, integrated backscatter measurements differentiated normal tissue from myocardium with mild or severe changes in rabbits with doxorubicin-induced cardiotoxicity[28] and normal from fibrotic and from calcified myocardium in hearts from Syrian hamsters with hereditary cardiomyopathy.[29] Subsequently, we found that acute myocardial ischemia immediately abolished the cardiac cycle-dependent variation of backscatter typical of normal myocardium[30] and that prompt reperfusion restored it.[31] In contrast, delayed reperfusion after tissue damage had become irreversible was associated with protracted and incomplete recovery of cyclical variation.[32] The results were not attributable simply to segmental thickening. Cardiac cycle-dependent variation of backscatter recovered earlier than wall-thickening. Thus, detection with backscatter imaging of return of cyclic variation should facilitate early differentiation of viable but stunned myocardium from irreversibly injured tissue subjected to ischemia and reperfusion.

Myocardial integrated backscatter is increased in regions of remote infarction.[26,33] Thus, backscatter imaging with measurement of cyclic variation can localize scar formation[34] reflected by marked blunting of the magnitude of cyclic variation. Acoustic properties giving rise to increased backscatter from regions of infarction were evident as well in observations by Parisi et al,[35] Shimazu et al,[36] Skorton et al,[37] and Schnittger et al,[38] who used diverse approaches to assess acoustic phenomena typical of zones of infarction.

Results in studies from our group in vitro[26] and in vivo[25] suggested that acoustical measurements based on the frequency-dependence of myocardial integrated backscatter can differentiate acutely ischemic yet still viable stunned myocardium from irreversibly injured tissue in zones of completed infarction despite comparable asynergy in segments of both types. Thus, both normal and acutely ischemic myocardium exhibit a frequency dependence of f^n, as opposed to values from segments with infarction, which demonstrate a frequency dependence of f^{n-1}. These relations have their basis in the Rayleigh scattering principle, according to which the sono-opacity of blood is expected to be dependent on the frequency to the fourth power of the incident soundwaves—a response reflecting the dominant size of scatterers in the tissue of interest. Because normal and ischemic myocardium are relatively devoid of large aggregates of scatterers such as collagen, they exhibit a frequency dependence of backscatter that differs from that in zones of remote infarction in which collagen content is increased.

In concert, results of studies both in intact laboratory animals and in vitro (in which interactions between ultrasound and myocardial tissue can be defined rigorously) have contributed substantially to the foundation needed for clinical applications of backscatter imaging.

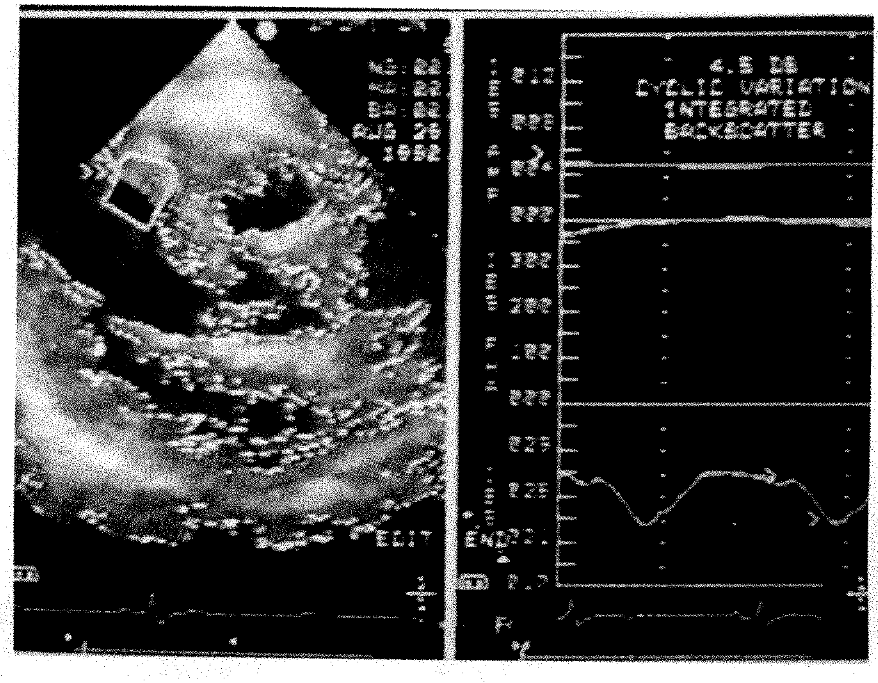

FIGURE 3. Integrated backscatter parasternal long-axis view, combined with automated boundary detection processing (*left*) with a region of interest placed in the midseptum (arrowheads). Quantitative integrated backscatter tissue data within the region of interest are being acquired continuously and displayed beat-by-beat (*right, bottom panel*) with the typical, physiologic diastolic-to-systolic decrease (variation; arrowheads) estimated to be 4.5 dB (*upper right panel*, integrated backscatter AMP). The *middle panel* displays the phase of the signal with respect to the QRS.

CLINICAL STUDIES

We and others have utilized integrated backscatter real-time imaging with a commercially developed system in normal volunteers[21,39,40] and in consecutively studied patients undergoing diagnostic procedures in the echocardiography laboratory.[41] Results with the M-mode–assisted approach demonstrated that the cardiac cycle-dependent variation of integrated backscatter averaged 4.5–6.0 dB in normal tissue in the septum and posterior wall evaluated with parasternal long-axis view. The same segments exhibited more variance in average values when results were obtained from short-axis or apical views,[21] emphasizing the importance of further elucidation of the influence of and compensations for the angle between the incident ultrasonic beam and the predominant direction of myocardial fibers in the segment interrogated.[42] We have previously demonstrated in studies of animals[43–45] that the anisotropic properties of myocardium markedly influence the magnitude of the cyclic variation of integrated backscatter. Thus, reduced backscatter, reduced cyclic variation, and increased attenuation are associated with parallelism between the direction of the beam and the predominant orientation of myocardial fibers.

Patients with dilated cardiomyopathy who are awaiting cardiac transplantation[39] exhibit markedly reduced cyclic variation (0.9 ± 0.8 dB in the septum and 1.8 ± 1.2 dB in the posterior wall), as do patients with temporally remote myocardial infarction. Zones of asynergy identified by conventional echocardiography exhibit diminished values of cyclic variation in contrast to that in normal regions, which exhibit typical, cardiac cycle-dependent variation of integrated backscatter.[46]

Patients studied within 24 hours of admission to the Barnes Hospital Cardiac Care Unit with acute myocardial infarction in progress exhibited marked blunting of cyclical variation of backscatter in zones of asynergy compared with values in normal segments.[47] Further, effective coronary thrombolysis with induction of patency of the infarct-related vessel was associated with subsequent, significantly increased cyclic variation in the same zones, despite their continued asynergy. Of note, abnormal wall motion per se (e.g., paradoxical septal motion after corrective heart surgery) does not distort detection of typical cyclic variation in normal, viable myocardium, as shown by results in children without residual evidence of heart disease after surgery to correct congenital heart disease.[48]

Of particular interest, results in recent studies in patients with insulin-dependent diabetes but no cardiac signs or symptoms showed that reductions in cyclic variation of myocardial integrated backscatter are present. Those patients with the most advanced noncardiac complications of diabetes were the same ones in whom the reduction of cyclic variation was most pronounced.[49] These results suggest that occult, structural alterations of myocardium in the diabetic heart can be detected with quantitative ultrasonic backscatter imaging before the appearance of any conventional signs or symptoms of cardiac involvement and hence at a time when the heart may be particularly amenable to protective measures.

Clinical studies performed at Stanford University have focused on detection of cardiac allograft rejection,[50] and characterization of myocardial hypertrophy.[51] Lattanzi and coworkers[52] have characterized hearts of patients with hypertrophic cardiomyopathy by measuring backscatter relative to the strength of signals from the pericardium and have demonstrated increased intensity of backscatter from myocardium in the hypertrophied hearts. The changes observed may reflect increased collagen or myocardial fiber disarray. In aggregate, the results of clinical investigations to date document the applicability of myocardial tissue characterization with analysis of radiofrequency signals and real-time imaging to detection and assessment of the severity of a variety of conditions.

USE OF QUANTITATIVE ULTRASONIC BACKSCATTER IMAGING FOR ON-LINE EDGE DETECTION

One of the fundamental characteristics of image processing presently required for real-time integrated backscatter imaging is averaging over a considerable interval, typically a 3 μsec time gate, along each A-line in the field of view. This procedure results in display of a significantly smoothed image with only minimal speckle and clear demonstration of the endocardial surfaces. Recently, image processing of this type has been employed to enhance the utility of previously developed edge detection algorithms[13] and to implement them in real time for detection and tracking of endocardial–blood boundaries.[14–16] When an on-line edge detection algorithm is interfaced with an operator-driven selection of a region of interest, the cardiac chamber areas (in cm^2), fractional area change (in %) and rates of change in area (in cm^2/sec) can be quantified and displayed in real time on a beat-by-beat basis. Results can be acquired readily in patients undergoing dobutamine stress echocardiography[53] or transesophageal atrial pacing.[54] Other studies focused on laboratory animals with heart failure,[55] changes in ejection fraction, and cardiac output in patients.[56,57] Thus, on-line edge detection with the use of backscatter imaging is remarkably effective in permitting instantaneous calculation and graphic depiction of ventricular dimensions and functional indexes in real time (Figure 4).

CONCLUSION

Ultrasonic backscatter imaging coupled with progress in 2-dimensional echocardiography and development of sophisticated algorithms for image analysis permit quantitative detection of acoustic properties of myocardium that reflect its physical state, structural characteristics, and behavior, as already shown in studies throughout the world. Further developments will undoubtedly advance our understanding of interactions between ultrasound and tissue. Results should complement the already useful information readily obtained by conventional echocardiography. Applications of backscatter image processing in clinical practice should facilitate on-line quantification of ventricular dimensions and function through automated edge detection previously not technically available. The convergence of 2-dimensional echocardiography and ultrasonic tissue characterization has already resulted in enhancement of the diagnostic

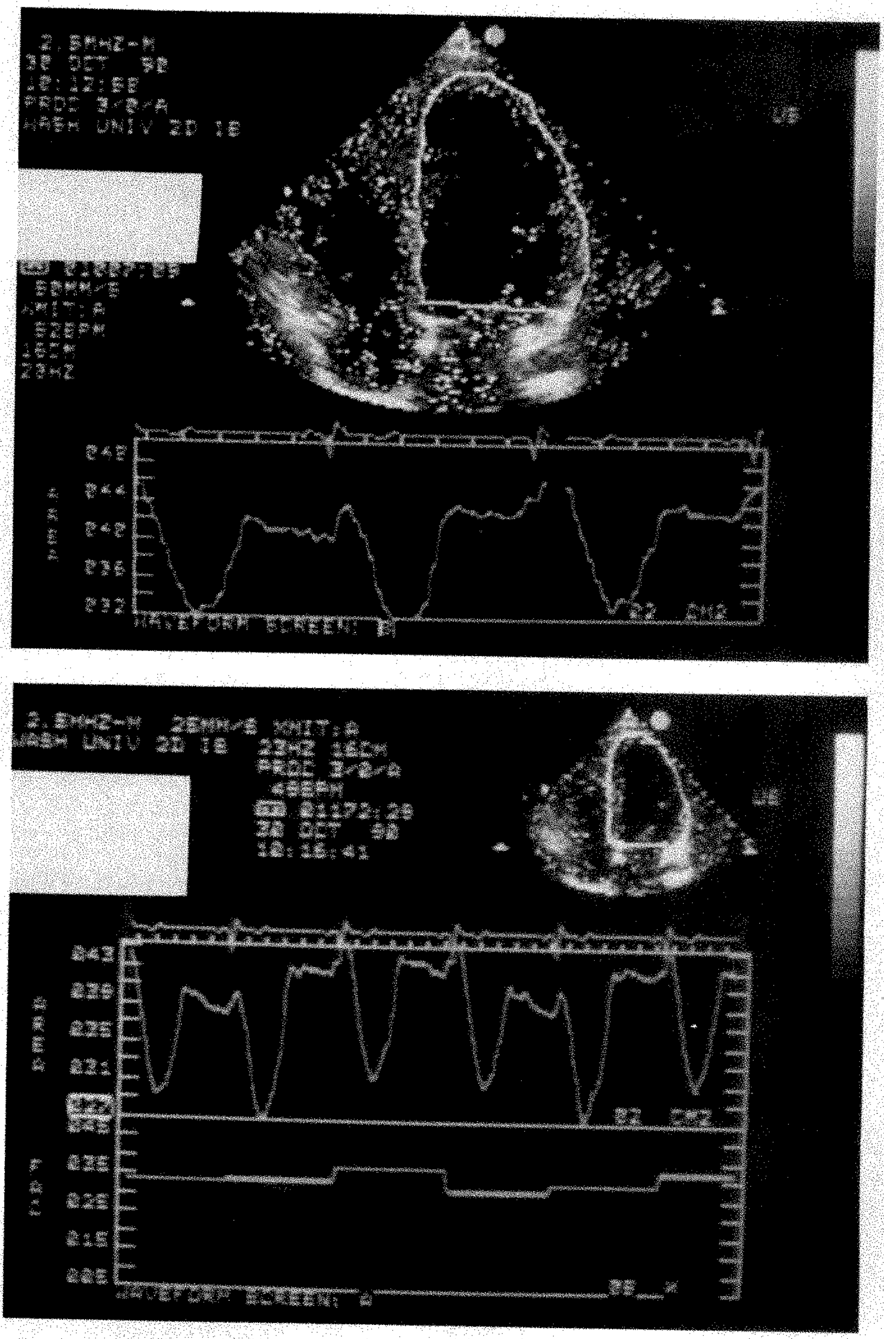

FIGURE 4. ***Top:*** **Freeze-frame (end-diastolic) automatic boundary detection 4-chamber apical image obtained by measurement of integrated backscatter with frame-by-frame delineation of the endocardial–blood interfaces derived from acoustic parameters. The instantaneous left ventricular cavity area is measured and displayed as a continuous signal with a calibration of 2 cm²/division.** ***Bottom:*** **In this format, the compressed 2-dimensional boundary detection image is in the upper right corner. The graphics depict beat-by-beat instantaneous left ventricular cavity area and calculated fractional area changes (FAC) in percentage units.**

power of noninvasive procedures for delineation of structural characteristics of myocardium and assessment of cardiac function.

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Recent Experience with Ultrasonic Tissue Characterization

Richard L. Popp, MD

The current effort in the research laboratory at Stanford University Medical Center attempts tissue characterization using the parameter of cyclic variation of integrated ultrasonic backscatter (CVIBS). This parameter is available using prototype equipment that concentrates on the relative change in ultrasonic backscatter rather than the absolute level of backscatter measured. The interobserver reproducibility is quite good. The magnitude of CVIBS is greater in the posterior wall than in the septum generally. There is a weak association of aging with the magnitude of CVIBS. Measurement of CVIBS in patients with uncomplicated pressure overload hypertrophy and those with hypertrophic cardiomyopathy shows values in the posterior wall to be similar for all groups; however, the values for the septum were significantly smaller in patients in both hypertrophy groups compared with normal subjects. Studies in human cardiac allografts for the recognition of acute rejection have been carried out using CVIBS. A decrease in the magnitude of this parameter during rejection, compared to the baseline level, was characteristically seen. Return to prerejection levels was not invariably seen. Among the different systems for ultrasonic tissue characterization, the current system using CVIBS has been successful in specific studies.

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The study of the interaction of ultrasonic (high frequency) sound waves and tissue has been evolving at Stanford over many years. The early work dealt with radiofrequency signal analysis from commercially available equipment. This was all aimed at the goal of a clinically useful process for differentiating normal from several types of pathologic tissue.[1–11] Although many of these techniques were successful, each had its individual problems and limitations, so that even the techniques of analysis have undergone drastic evolution. Some of these techniques should not be discarded but simply are not available on current implementations of commercially available equipment.

Most recently, we have been working with prototype equipment that permits measurement of the amplitude of ultrasonic signals backscattered from the myocardium, integrated over a broad band of frequencies. This is the system developed by Miller and Perez at Washington University and discussed in the previous article in this symposium. The data to be presented are from recent work using an implementation of this system that is analogous to M-mode recording of the echocardiogram but using the parameter of cyclic variation of integrated ultrasonic backscatter (CVIBS). Because of the problems of developing a standardization for this parameter to compensate for the variable attenuation of the sound in different patients, it is necessary to look solely at the cyclic variation of this integrated backscatter (IBS) over the cardiac cycle.

METHODS

Ultrasonic backscatter instrumentation and technique: IBS was measured with a modified commercially available real-time, 2-dimensional imaging system (77020AC, Hewlett-Packard) equipped with a 64 or 128 channel phased array 3.5 MHz transducer. With this system, 2-dimensional and M-mode images of IBS as well as conventional echo amplitude images are obtained. In the IBS imaging mode, the received ultrasound signal is

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amplified, mixed into an appropriate intermediate frequency, phased, and delayed. Different from a conventional imaging system, the unprocessed radiofrequency signal is accessed with the IBS processor to produce a continuous signal that is proportional to the logarithm of IBS. In the calculation of the logarithm of IBS, the integration time is 3.2 μsec, and the dynamic range of the IBS processor is >40 decibels (dB). Measurements of IBS in absolute terms cannot be obtained with this system because calibration of the absolute time-averaged IBS level is not available. However, if IBS is measured at 2 different instants (for example, at end-diastole and end-systole) in the same area, the logarithm of the ratio of the IBS energies at these 2 instants is available quantitatively (in decibels) by calculating the difference between them. Although the instantaneous value of IBS is related to gain settings, the magnitude of cyclic variation of IBS (in decibels) is essentially independent of transmit power over the range of transmit power employed in this study.

The transmit power and time-gain compensation settings were adjusted so that the myocardium was filled with a medium-to-low–level signal that showed the largest cyclic variation in the visual brightness (that is, maximal brightness in late diastole and minimal brightness in late systole). The gain controls were not adjusted equally throughout the sector field and, therefore, each depth had different gain emphasis. However, once they were adjusted initially for each study, they were kept constant throughout each study. No attempt was made to standardize instrument adjustment among the subjects because only the relative change in IBS in each patient was of interest, not the absolute level of this variable.

Each subject rested in a left lateral decubitus position and breathed in a relaxed fashion during the ultrasound examination. The transducer was placed at the parasternal border and positioned to provide echo amplitude imaging of the long- or short-axis view of the left ventricle. The switch to provide the IBS image was then toggled. The M-mode IBS image was obtained by positioning a cursor on the 2-dimensional image to select the region to be measured in the interventricular septum and left ventricular posterior wall, and the M-mode IBS images were frozen for the system's microprocessor analysis on screen. The value of IBS (in decibels) in an area of interest is obtained by placing a rectangular-shaped area of interest indicator of variable size anywhere on the frozen M-mode IBS image. The serial time-varying changes in the amplitude of IBS, on a relative scale, are obtained by tracing the area of interest from left to right (representing time) in the frozen M-mode IBS image. This is displayed as a curve of IBS versus time.

Data analysis: Temporal changes in IBS were measured by tracing out the area of interest along the myocardium between the specular high amplitude signals from endocardial layers for the septum and between signals from endocardial and epicardial layers for the posterior wall in the frozen M-mode images. The size of the area of interest most consistently selected in this study was approximately 2.8 mm × 80 msec. When the area of interest could not be traced free of the interference of bright specular echoes, a smaller area of interest was selected. From the line plot of time versus amplitude of IBS, the magnitude of cyclic variation of IBS was determined as the difference between minimal and maximal peaks. This IBS measure was obtained on-screen using the software resident in the ultrasound scanner. The time interval from the onset of the QRS wave of the electrocardiogram to the minimal value of IBS was also measured manually on the hard copy of the line graph of time versus amplitude of IBS. Values averaged over at least 3 beats were provided for quantitative analysis.

Reproducibility: Observer variation was estimated by calculating mean values and standard deviations of differences, as well as absolute differences between observations. Mean values of absolute differences between observations were slightly but not significantly smaller for the posterior wall than for the septum. Mean interobserver variation for the magnitude of cyclic variation of IBS in the septum was 0.2 ± 1.4 dB[12]; the same value for the left ventricular posterior wall was −0.1 ± 1.1 dB. Intraobserver differences for the septum and posterior wall, respectively, were 0.1 ± 1.0 and 0.1 ± 0.6 dB. The absolute difference in interobserver measurements was 1.2 ± 0.8 dB and for the left ventricular posterior wall, 0.8 ± 0.6 dB. The intraobserver variability for the septum and posterior wall was 0.8 ± 0.6 and 0.5 ± 0.4 dB, respectively.[12]

Initial studies[12] in 45 subjects without evidence of heart disease, although carefully screened for it, showed that 5 subjects were excluded because excellent conventional and IBS images were not obtainable. In the remaining 40 subjects, aged 22–71 years (mean 41 years), there seemed to be differences in the CVIBS of the septum and posterior wall. The magnitude of CVIBS was greater in the posterior wall than in the septum in 34 of 40 subjects, of equal value in these 2 areas in 3 subjects, and of greater value than in the septum in the remaining 3 subjects. The mean value of the magnitude of variation of IBS for the posterior wall was significantly greater than that for the septum (6.3 ± 0.8 vs 4.9 ± 1.3 dB; $p < 0.01$).

There was a weak but statistically significant correlation between the magnitude of cyclic variation of IBS and age with respect to the posterior wall ($r = -0.47$; $p < 0.01$), but not for the septum ($r = 0.21$; difference not significant).[12] These data are interesting, since experimental studies in animals have shown that the magnitude of CVIBS parallels the regional differences in contractile performance throughout the left ventricle. Because contraction patterns have been demonstrated to be greater in the posterior wall than in the anterior wall or in the septum, in normal subjects, the difference in the magnitude of CVIBS between these portions is consistent with this finding and may be partly explained by it. The percent systolic wall thickening measured by M-mode echocardiography in this study was 67 ± 19% for the posterior wall and 52 ± 19% ($p > 0.01$) for the septum. It should be noted here that data from our laboratory[7,9,13] and others[14–16] suggest that CVIBS is not solely related to myocardial thickening, and the regionality of the variation of IBS probably is due to other factors such as regional variations in fiber architecture, structure or geometry of muscle fibers, and other properties of the myocardium that are not yet elucidated.

The weak inverse correlation between the magnitude of CVIBS and age for the posterior wall in normal subjects is interesting. Although accumulations of lipofuscin in the myocyte and an age-related increase in the number of small foci of fibrosis in the myocardium have been postulated, these changes are not uniformly found in all studies. Thus, the age-dependency of this CVIBS may not reflect changes in cardiac histology. Contractile performance has been considered to be little affected by age, in contrast to relaxation properties and diastolic stiffness of the ventricle. Changes in structure and geometry of individual muscle fibers or other changes in properties in the myocardium with aging may account for the age relation of the magnitude of CVIBS; however, in the study described it was not possible to determine which factors contribute to this relation. Such a relation was not found for the septum. In many of these normal subjects there was difficulty in measurement of the septum because of its dimensions and this, along with technical problems, may be partially responsible for the differences between the 2 portions of the myocardium. If the 6 subjects with a magnitude of CVIBS of ≤3 dB were arbitrarily excluded, a weak, but statistically significant correlation between age and the magnitude of CVIBS was also present in the septum ($r = 0.5$; $p < 0.01$; $n = 34$).

Studies in human hypertrophied hearts in vivo: Studies in 12 patients with uncomplicated pressure overload hypertrophy and 13 patients with hypertrophic cardiomyopathy were undertaken to explore ultrasonic tissue characterization further. Sixteen normal subjects served as the control group.[17] The magnitude of CVIBS for the posterior wall was 6.0 ± 0.9 dB in normal subjects, 5.7 ± 0.8 dB in patients with uncomplicated pressure overload hypertrophy, and 6.7 ± 2.1 dB in the patients with hypertrophic cardiomyopathy. There were no significant differences among any of these groups. In contrast, the magnitude of CVIBS for the septum was significantly smaller in the patients with uncomplicated pressure overload hypertrophy (2.8 ± 1.3 dB) and in the patients with hypertrophic cardiomyopathy (3.1 ± 2.3 dB) than in normal subjects (4.9 ± 1.0 dB; $p < 0.05$ for both comparisons). There was a weak but statistically significant correlation between percent systolic thickening of the myocardium and CVIBS ($r = 0.67$; $p < 0.01$; $n = 82$). These striking regional alterations in the magnitude of the CVIBS were especially interesting in some details. Although the magnitude of CVIBS for the posterior wall was essentially equal in all patients, there was at least 1 patient with hypertrophic cardiomyopathy with an excessively high CVIBS. The range of magnitude of CVIBS in the septa of the hypertrophic cardiomyopathy patients was 0–7.5 dB. The relation between percent systolic thickening of the myocardium and magnitude of CVIBS was quite interesting, since as the percent systolic thickening of the wall decreased, the magnitude of variation of CVIBS tended to decrease. This was especially true at percent systolic thickening <40%. This gave a curvilinear relation and suggests that at <40% systolic thickening, the contraction of the myocardial elements has a direct relation on the magnitude of CVIBS. Again, detailed analysis of the data is interesting, since the magnitude of CVIBS in the posterior wall was normal in some patients with decreased systolic thickening of the wall. This again emphasizes that changes in acoustic properties of the posterior wall reflected by CVIBS are not directly measuring changes in systolic thickening of the wall alone. A wall-thickness index was calculated as the value of wall thickness at end-diastole divided by left ventricular diastolic dimension for all patients. As wall-thickness index increased, magnitude of CVIBS tended to decrease, and there was a weak but significant correlation between these 2 parameters ($r = 0.53$; $p < 0.01$; $n = 82$). There was a closer relation between these parameters in the pressure overload hypertrophy group ($r = -0.61$; $p < 0.01$) and in the hypertrophic cardiomyopathy group ($r = 0.72$; $p < 0.01$), with different linear regression data for these 2 groups. In fact, for similar wall thickness indexes, the CVIBS tended to be larger in patients with hypertrophic cardiomyopathy than in patients with pressure overload hypertrophy.[17] Once again, it is important to state that although CVIBS is somewhat related to wall thickening, it also seems to be affected by factors such as alteration in fiber architecture, structure or geometry of muscle fibers, and/or other properties of the myocardium that may be different in pressure overload hypertrophy and idiopathic hypertrophy related to hypertrophic cardiomyopathy.

Studies in human cardiac allografts for the recognition of acute rejection: Our original studies[18] included 23 allograft recipients and 18 normal subjects. In each cardiac allograft recipient, 1–8 (mean 4) CVIBS studies were obtained, each within 24 hours of right ventricular endomyocardial biopsy that was performed for rejection surveillance. The magnitude of the CVIBS in the posterior wall was 5.98 ± 0.9 dB in normal subjects and 6.2 ± 1.3 dB in 17 cardiac allograft recipients without previous or current histologic evidence of acute rejection. These data were not significantly different between the 2 groups. The magnitude of CVIBS in the septum was 4.8 ± 1.1 dB in normal subjects and 3.8 ± 2.0 dB in 15 cardiac allograft recipients. This also was not significantly different from the normal subjects. A significant decrease in the septal CVIBS was observed in cardiac allograft recipients with left ventricular hypertrophy defined as wall thickness of ≥13 mm compared with normal subjects (2.6 ± 1.7 dB; $n = 8$; $p < 0.05$). CVIBS studies were done before and during moderate acute rejection in 11 allograft recipients (14 episodes).[18] During moderate acute rejection the magnitude of the CVIBS decreased from 6.7 ± 1.3 to 5.1 ± 1.4 dB in the posterior wall ($n = 14$; $p < 0.05$) and from 4.1 ± 2.1 to 2.9 ± 1.8 dB in the septum ($n = 12$, $p < 0.05$). These data again suggest the magnitude of CVIBS of the septum is different in cardiac allografts with cardiac hypertrophy compared with normal subjects. Of special interest is the finding that acute cardiac rejection in humans is accompanied by an alteration in the acoustic properties of the myocardium. This change is detectable by serial measurement of the CVIBS of the septum and the posterior wall. It is especially useful when done in individual patients followed serially.[18]

Using endomyocardial biopsy as the standard, and using moderate or severe rejection as positive findings on the biopsy, it was possible to compare the CVIBS by defining a rejection episode as ≥1.5 dB decrease in the magnitude of CVIBS of the posterior wall or ≥1.0 dB decrease in the magnitude of the CVIBS in the septum. By these criteria, the change in CVIBS had a sensitivity of 86% and specificity of 85% for diagnosis of rejection using data from the posterior wall and a sensitivity of 83% and specificity of 71% using data from the septum.[18] Once again, data from this study suggest that CVIBS is not solely associated with rejection-related indexes such as myocardial thickening. It is well known that interstitial edema, hemorrhage, or both can occur in the presence of cardiac rejection. The possible myocardial ischemia associated with rejection—and/or alterations in water content associated with rejection—also may partially account for the changes in CVIBS associated with acute cardiac rejection.

The decreased magnitude of the CVIBS during rejection did not return to the prerejection values in all cases after resolution of the episodes.[18] It is known that scar or interstitial fibrosis formation follows myocyte necrosis, and these irreversible changes in the myocardium may partially explain this finding. The mechanism of the changes in the variation of CVIBS associated with rejection and its resolution are still unclear. Disagreements between CVIBS measurements and biopsy data occurred in 5 of 34 studies in the posterior wall and 7 of 29 studies in the septum. Biopsy specimens were sampled from the right ventricular apex and septum, and CVIBS measurements were performed in the left ventricular walls. The rejection process does not seem to affect left and right ventricles to the same extent, nor is the severity of rejection uniform throughout the ventricular wall. Inhomogeneity of the rejection process and biopsy sampling error can partially explain the disagreement in some patients. Although Doppler echocardiography or magnetic resonance imaging might provide more global estimates of rejection, they have not been widely applied and were not used for comparison at the time this study was done.

Video analysis for ultrasonic tissue characterization: Several groups have used image analysis of the video-processed signal to attempt characterization of myocardial tissue using ultrasound.[19–22] Data from our own laboratory, using acoustic microscopy at 200 MHz, suggest that myocardial cells in normal subjects and patients with cardiomyopathy are organized with spacing that is too small to be reflected by the pattern of the ultrasonic image.[23] The wavelength of ultrasound at 5 MHz is approximately 300 μm whereas the parameters calculated from acoustic microscopy suggest a mean autocorrelation length of 37 ± 18 μm with a maximum value of 92 μm. In myopathic specimens the mean value was 52 ± 19 μm with a maximum of 100 μm. Our data suggest that the changes in structure between normal and myopathic myocardium are significant, but on so small a scale in relation to the wavelength of clinical ultrasound that there will be changes only in the intensity of the backscattered signal and not in the pattern of speckle making up the image. Nevertheless, clinical experience shows that some conditions apparently are reflected in the appearance of the myocardium with clinical ultrasonic instruments operating at 2.5–5 MHz. This is especially true for some patients with hypertrophic cardiomyopathy and most of those with amyloidosis.[24–26] Thus, there are some features of the architecture of these abnormal tissues that show up in the ultrasonic image. Muscle fiber orientation also is reflected by the echocardiographic appearance of the myocardium.[13] Currently, these areas are not well understood.

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Discussion V: Tissue Signature

Dr. Harvey Feigenbaum (Indianapolis, Indiana): Will each panelist please state his current perspective regarding tissue characterization?

Dr. Sanjiv Kaul (Charlottesville, Virginia): A major problem that transthoracic echocardiography has to overcome is interpatient acoustic variability. It is possible to use the same patient as the control preinfarction and postinfarction, but being able to obtain absolute quantitative information with different acoustic windows is an almost insurmountable problem. Perhaps if statistics, kurtosis, and standard deviation were combined into an algorithm in some way with artificial intelligence, then we might be able to make accurate tissue characterization.

Dr. Feigenbaum: How much of a problem is the signal-to-noise factor and would a more invasive acquisition of images, either transesophageal or intravascular, be a major factor in improving the ability to identify tissue?

Dr. Julio Pérez (St. Louis, Missouri): Signal-to-noise ratio is a relevant issue. In the operating room, for example, with a 5 MHz transducer that can be coupled to this system, we can obtain images that are much better and a yield that is higher: nearly 90% in a random sampling of operating room cases. The key issue that still remains, however, is interpatient differences. How can we control for the day-to-day variability in the same individual, or for the differences from one patient to another? If there were some kind of internal standard or quantitation available in the image, such as the blood pool, it could potentially be used to standardize the information. With a modified imager, values can be obtained, but if there is no reliability in how constant they are from day to day or individual to individual, one cannot make accurate comparisons.

What I just mentioned about the quantitation used in blood is something that has considerable clinical potential. In essence, blood has a very low and stable backscatter over a wide range of hematocrit levels. However, because the backscatter of blood is much lower, even below that of tissue, it has been thought that the scattering of blood can be obtained from the Doppler signal. If it is possible to observe a Doppler shift in blood moving in the vicinity of the targeted region, we could potentially use that as a uniform standard to obtain these measurements.

Dr. Richard Popp (Stanford, California): To extend the issue a bit further, I think the major problem Dr. Kaul raises is the question of how to standardize attenuation across the chest wall. If we could use a parameter like blood, which would be the easiest thing, it would be possible to standardize values each time and, therefore, eliminate the problem. The other point that was raised is the possibility of tissue characterization using intravascular probes. I think that can be done but it must be treated in a different way because the radiofrequency signal from the probes almost assuredly will reflect differences in structure. I am not sure about assessing chemical content, but regarding fibrosis, fibrofatty plaque, or calcification, I think we should easily be able to characterize these because we are not looking at all the complexities of muscle, but rather fairly well-described and accessible kinds of structure.

Dr. David Skorton (Iowa City, Iowa): Backscatter is quite stable over a clinically applicable range of hematocrit levels, which indicates to me that the technique shows promise. It has provided a better understanding of the basic acoustics, which someday should translate into improved images and improved ways to perform echocardiography. This is the most tangible effect that has come from tissue characterization research since it began in 1971–1972.

The tissue characterization that we do in cardiology can be divided into 2 broad categories: indirect and direct tissue characterization. The indirect type involves what we do clinically, wall motion and wall thickness determinations. Direct tissue characterization can be divided into 2 subcategories: structural and metabolic. The kind of characterization that echocardiography involves is the structural type, which is based on abnormalities of myocardial architecture and to some degree the definition of abnormal substances. Metabolic characterization parameters include perfusion, substrate uptake in metabolism with positron emission tomography (PET), phosphorus-31 content, water content, intracelluar pH, and enzyme kinetics with magnetic resonance (MR). Metabolic tissue characterization will have more clinical applications in the future.

There are 4 methods that can generally be used for tissue characterization: ultrasound, radionuclide, computed tomography (CT), and MR. Ultrasound can provide morphology, indirect tissue characterization, and structure. Radionuclide and MR studies are used for metabolic characterization. When CT scanning was used initially, it was thought to be possible to do tissue characterization directly by evaluating CT number to CT number or x-ray absorption as related to electron density. However, it did not prove to be as useful in the heart as in the brain and other areas.

The 2 most important parameters that have already been used quantitatively for tissue characterization are both types of perfusion measurements. With PET scanning, using a variety of positron emitters that are freely diffusible across membranes, you can evaluate blood flow. In the near future, if contrast agents can provide even semiquantitative estimates of perfusion, this would be a major advancement in tissue characterization.

I also believe the problems with intersubject acoustic variability must be overcome. In one study in normal subjects cyclic variations ranged across 0–7 dB. That much intersubject variability makes it difficult to get absolute quantitative information, which is similar to what we have with hematocrit levels. At least if we can establish regional relative differences, it would be a step toward standardization and quantitation of measurements. Thallium scans do this imperfectly, and I believe that echocardiography needs to improve in this area.

Dr. Pérez: I think we should consider other methods for doing tissue characterization, for example, the scatter number density method, which refers to the number of scatters per volume. In a particular model of backscatter equipment being studied, the investigators believed that the scatter number density would differentiate and provide the actual physical characterizations of the median. In other words, scatter number density will provide tissue characterization of the myocardium.

The cyclic variation factor previously mentioned also depends on the "speckle" or noise, which is partly a function of the particular equipment being used. However, part of that also is the backscatter. There is clearly a need to make refinements, and scatter number density is a technique that may enable accurate differentiations.

Dr. Richard Meltzer (Rochester, New York): When the differences between tissue states are patently obvious, there must be a method of quantitating these variations. Although many of the effects that we see are produced by the instrument, other effects involve the actual architecture of the tissue. To date we have not found a way to quantitate these effectively, and I believe this is an area that should be explored.

Dr. Pérez: One of our difficulties is that, historically, the development of this technology has taken time, at least 10–15 years, until these techniques can become clinical tools. In addition, industry must play a large role because, unfortunately, as much work as we can do in a single institution or even through collaboration, individuals do not have the resources to develop an imaging system without industrial support.

Dr. Feigenbaum: Absolutely. No clinically accepted technique in echocardiography took <10 years from the time of inception to the time it was generally accepted for use. Many techniques took longer, but none took <10 years, including transesophageal, Doppler, color, M-mode, and 2-dimensional.

Dr. Kaul: None of these are simple measurements. Looking at the myocardium, whether with backscatter or with video, is a complex procedure. Therefore, I think the more parameters we can extract using different methods and then combining them in a kind of statistical formulation will prove to be clinically useful. The statistical information can be principal-components analysis, cluster analysis, or anything that separates normal from abnormal.

Regarding transplant rejection, Dr. Popp, does microvascular damage occur during early phases of rejection? Would it be possible to inject small bubbles and show heterogeneity in the myocardium?

Dr. Popp: One of the first effects is endothelial damage within the vessels, which allegedly leads to much of the edema that is seen. However, this occurs over a very long time course. When you reanalyze the dimensions of the cellular separation on a microscopic level, for example, these are not of a magnitude that you would expect would affect the 5 MHz transducer we are using.

Dr. Kaul: That is significant because endothelial damage causes these bubbles to "stick" in the vasculature. We see that with cardioplegia the bubbles do not pass through rapidly because of endothelial damage. To enhance the possibility of detecting rejection early, it is important to use some kind of contrast medium.

Dr. Navin Nanda (Birmingham, Alabama): I think there is also a problem with the "gold standard" by which we grade rejection. It is either mild, moderate, or severe, but analyzing myocyte necrosis is a subjective matter. We can give the same biopsy to 2 different pathologists and they will come up with different results. At the same time, we classify what they would term moderate and severe rejection as acute rejection, and if it is mild rejection, we consider that to be no rejection. Finding an alternative method for the early detection of rejection would be an important advancement.

Dr. Popp: The pathologists do not believe that biopsy is a great gold standard, but the surgeons who rely on it say that it is. You get so used to using it that no one questions it. However, when an abnormality occurs with Doppler and the biopsy is negative, we know we have to biopsy again soon because it will be positive.

Dr. Julius Gardin (Orange, California): We use graded backscatter to do edge detection, and we see fractional change beat-to-beat in the clinical situation. Do these algorithms take advantage of temporal averaging that may not be available on a single beat but may be available 3 beats earlier?

Dr. Pérez: Such temporal averaging is not available over several beats. In the present permutation, every cardiac cycle is analyzed individually. It is possible to use M-mode scanning and simply slow down the display rate and average over 10 cardiac cycles, and in this way you can have a picture that has 10–15 beats in 1 visual image.

Dr. Popp: That is not exactly correct. What Dr. Geiser has traditionally done with this technique is to use one frame as a guide as to where the signals are going to be on the next frame. In other words there is a region of interest that you delimit. Your eye tells you where to draw a line, which then limits the area that it views; essentially it connects its own dots. This is an imperfect technique, which is currently undergoing refinement.

Dr. Skorton: I would like to expand on this process. For one thing, it is based entirely on measurement of backscatter and differential amplification of the signal. There is a very large differential in backscatter from the blood vs the myocardium. Originally, a simple analog comparator circuit was used, and if the backscatter was above a certain subjectively chosen threshold, it was considered to be tissue. If it was below that threshold, it was considered to be blood or noise. If it was the latter, then we did not amplify very much, and not much gain was applied to it. However, if it was tissue, a higher gain value was applied, so it then became a binary decision: A dichotomous bi-stable image appears, and on the junction between those images (between the levels of backscatter, high vs low, on vs off), a dot was inscribed on every line with a video overlay of where that change occurred.

There are 2 important aspects to the technique: (1) knowing how to obtain the best image and knowing how to manipulate the gain settings, and (2) limiting the search to an observer-selected area makes the algorithm appear better because much of the irrelevance that might otherwise be seen is eliminated. The technique seems to work in perhaps 50–60% of all patients, and we can get data that seem reliable in defining the edge points. Beyond this, we still must decide how to deal with the contours and whether it will be a subjective semiquantitative scoring system or some quantitative method. Finally, we have to define normality and determine where the edges are and what the contours do.

Dr. Popp: I agree. I also believe the kind of fractional area change that we get from this technique is as good as radionuclide studies, which are fuzzy. We are getting yields that are much higher than those Dr. Skorton mentioned.

Dr. Feigenbaum: It is not yet a perfected technique, but it is clearly a step forward. I am sure with a little more work, it will soon be a clinically useful technique.

Participant: Do you have right ventricular backscatter data or left ventricular biopsy material? If I recall, the most consistent cyclic variation was in the part of the heart that usually is not biopsied.

Dr. Meltzer: Right. We do not do left ventricle biopsies, but we do get biopsies from the area where the bioptome is placed. When the procedure is done from the neck, it goes down to the apex of the right ventricle. However, we sometimes have difficulty because when we sample a lot all we get is scar. The variation that we measure is the septum and posterior wall. Several studies have revealed tremendous patchiness of the rejection process. The sampling area is one of the problems with biopsy, which is why our data are much less than perfect.

Dr. Edward Geiser (Gainesville, Florida): Automated border tracking has current importance because, as Dr. Parisi said, we are being driven by demands from the marketplace for practical applications. Obviously, this is a major step forward because it can also enable greater quantitation for echocardiography. "Automated" in this sense means that there is no region of search defined by an observer. Therefore, values are comparable among subjects, which can ensure standardization and reliability. The same steps that are necessary for the preprocessing of video images are also necessary for backscatter preprocessing. Preprocessing itself and edge detection are lower–intermediate-level operations designed to enhance indiscriminately edges in the image. "Indiscriminately" here is a mathematical term that means no matter where the area of brightness is located on the image. Whether it is over tissue or the side lobe artifact, the edge is enhanced. If you turn up the gain and produce something in the middle of the image, it will have an edge around it and that happens with or without using backscatter. There are different methods of processing the image with increasing sizes of various mathematical operations, which utilize both the epicardium and endocardium.

Boundary detection itself is a high-level decision-making process that rejects unwanted edges, retains the desired edges of all those enhanced in the image, and then fills in the gaps where there is inadequate information. To compensate for incomplete information, you can sometimes make a logical decision across a gap. If that is not possible, you might use the epicardium to help make that decision.

Dr. Popp: Dr. Geiser, it seems to me that the difference in backscatter between blood and tissue gives a much cleaner edge and larger signal, so that at least empirically where you think you see noise with your eye, the backscatter does not pick up. The edge is being tracked differently, so apparently there are real differences between the video-processed image and the backscatter image.

Dr. Geiser: That is right. I think the way in which the thresholds are set in the backscatter image can also introduce problems. If you turn up the gain and something is perceived as tissue, you get very nice crisp edges around noise.

Participant: That is the signal-to-noise ratio. That is how robust the process is.

Dr. Geiser: As Dr. Pérez also mentioned, because of the averaging across the wall in the radiofrequency signal, you also have a more blurred image. Therefore, we have to take into account what has been done to the edge position.

Dr. Pérez: We use a saline microbubble contrast medium, and not Albunex, in our studies. In terms of injecting saline microbubbles to outline endocardium on conventional images, my first reaction is that higher intensity would bring the image closer to what the endocardium or the myocardium really is. Developing an algorithm to measure a cavity would somewhat defeat that purpose.

Dr. Kaul: It depends on how you intend to detect the edge. You could be going inward; most echocardiographers go from the center outward, or you can come from outward to inward as well. There are a few ways to proceed, but if there is a homogeneous contrast effect, then I believe the endocardium at least is very well perceived. The gradient can be seen much more clearly with an adequate amount of contrast in the ventricle, which is the way we do ventriculograms. I am optimistic that with both digital image processing and contrast that we will be detecting edges automatically far more often than without contrast.

Dr. Geiser: I am sure that we have all had the experience of looking at a 4-chamber view when color is turned on and you see that the endocardium is missing. I think that another way to consider doing it is with the flow of the contrast, color, and the Doppler signal. Try to give yourself some clues as to where the endocardium is. This is another way to anchor yourself to know whether you are at the right point for endocardium.

Dr. Feigenbaum: Will your algorithm detect a color-flow myocardial image?

Dr. Geiser: When I set my region of interest, I can then tell whether the process is working correctly or not. Recently, we had a defect in the circuit and we knew it because, suddenly, I could see the endocardium, and we were not supposed to be tracking it. Setting the region of interest is another gauge to indicate whether the system is functioning correctly in this early stage of development.

Dr. Skorton: This system runs along each line of sight the way the ultrasound data are gathered, which can be both a plus and a minus. The advantage is that you are getting the data the way the machine actually receives them. The disadvantage is that it is mathematically indiscriminate. Wherever there is a change in backscatter along a line in the actual resolution, there will be a change in the data you receive. My prediction is that this machine could pick up color flow and many other things that cause a change in backscatter across that threshold.

Dr. Pérez: This is true, but if your goal is to identify the endocardium, and the conventional image is obviously present, you would turn off the borders. We do accept data as reliable if we turn the borders off, and we see that the conventional image shows as endocardium. No one is going to turn up the transmit and make the blood pool obviously echogenic because that would defeat the purpose. The operator still must interact with the machine while exercising judgment and control.

Three-Dimensional Echocardiography: Techniques and Applications

Robert A. Levine, MD, Arthur E. Weyman, MD, and Mark D. Handschumacher, BS

Current echocardiographic devices provide only 2-dimensional views of the heart. To appreciate 3-dimensional structural relations, therefore, requires mental reconstruction of 2-dimensional views by an experienced observer. Our ability to answer new questions about the heart could be increased if 2-dimensional images could be combined to display 3-dimensional relations. Such 3-dimensional reconstruction would permit analysis of structures of unknown or complex shape and the noninvasive quantification of cardiac chamber size and function without making geometric assumptions. To overcome previous limitations, mechanisms have been developed for automated integration of images and positional data during routine echocardiographic scanning, thereby greatly enhancing the efficiency and application of image reconstruction. Refining the diagnosis of mitral valve prolapse has presented a uniquely 3-dimensional problem requiring information previously unavailable from the 2-dimensional technique. To date, 3-dimensional studies have demonstrated that the mitral valve is saddle-shaped in systole, so that apparent superior leaflet displacement in the mediolateral 4-chamber view, often seen in otherwise normal individuals, lies entirely within the bounds defined by the mitral annulus and occurs without leaflet distortion or actual displacement above the entire mitral valve. Other applications of 3-dimensional image reconstruction include calculation of ventricular volume and ejection fraction by transthoracic or transesophageal scanning without geometric assumptions; improving the standardization and accuracy of 2-dimensional measurements by improving spatial appreciation; and 3-dimensional reconstruction of vascular walls to guide interventions. In the future, systems for acquiring multiple views more rapidly by parallel processing and improving endocardial border extraction should allow more routine application of 3-dimensional methods as the next stage in the evolution of cardiac ultrasound, thereby expanding the range of questions that can be answered. Achieving these goals will depend, in large measure, on persistence in developing the necessary technology.

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As in the history of science generally, advances in our understanding and ability to use echocardiography to answer clinical questions have been predicated on technologic progress. Over the past 2 decades, the diagnostic power of echocardiography has increased dramatically as we have progressed from M-mode to sector scanning, added Doppler and flow mapping, and broken through the barrier imposed by the chest wall. Our ability to answer new questions could be further increased if 2-dimensional images could be combined to display 3-dimensional relations; yet we remain largely limited to a 2-dimensional universe. To appreciate 3-dimensional structural relations, therefore, requires mental reconstruction of 2-dimensional views by an experienced observer. In addition, quantitative measures of cardiac chamber size and performance, such as ejection fraction, must be derived from 2-dimensional data, subject to an observer's mental geometric assumptions, which are least accurate when most needed, as in ischemic heart disease with regional wall motion abnormality. Thus, although this process may be satisfactory for structures of known and regular shape, such as the right ventricle and complex congenital heart defects, 3-dimensional reconstruction could eliminate the need for making geometric assumptions and thereby facilitate accurate evaluation of chamber size and shape, ventricular func-

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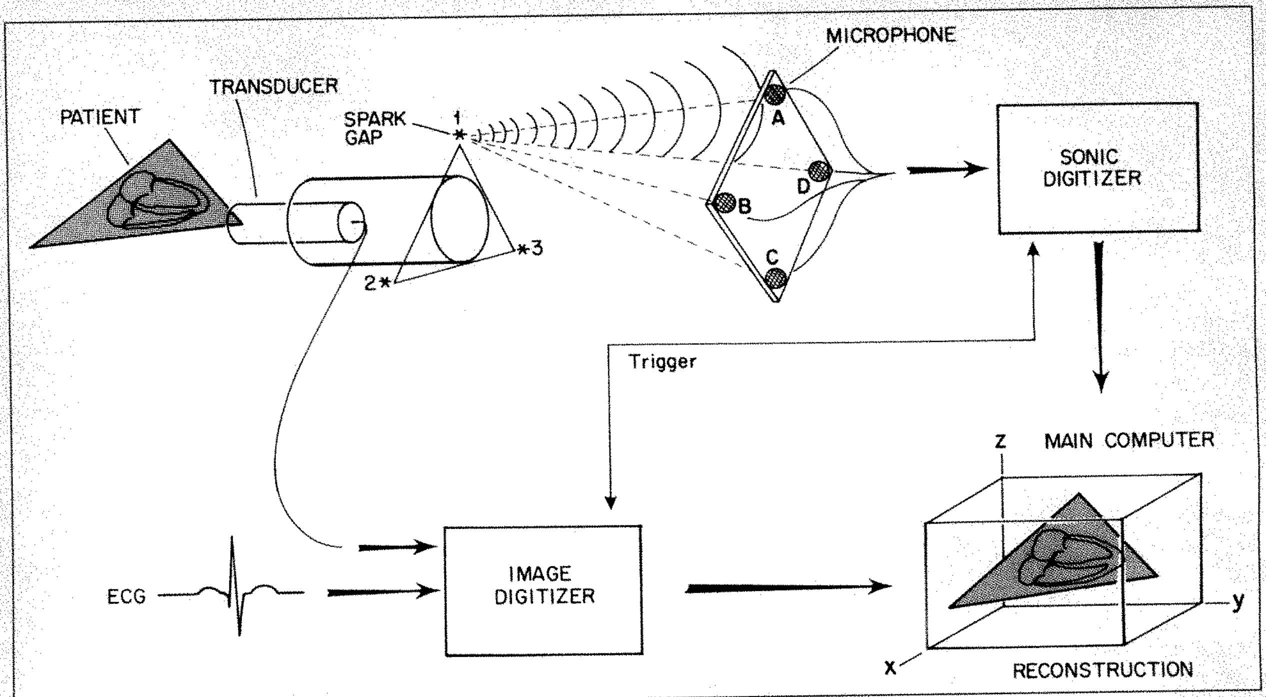

FIGURE 1. Schematic of reconstruction technique. The actual position of the tomographic image, indicated in the upper left-hand corner, is reproduced by the computer in a rectangular coordinate system (lower right). This is achieved by combining digitized video images (image digitizer) with their spatial locations obtained by the spark-gap triangulation system (sonic digitizer). The spark gaps lie on a plate attached to the back of the cylinder at the corners of an equilateral triangle. (Reprinted with permission from *Circulation*.[19])

tion, and complex structural defects. It would also allow quantitative description of structures whose surfaces do not form enclosed volumes, such as valve leaflets; this would be important in establishing mitral leaflet position relative to the anulus, thereby allowing us to refine criteria for mitral valve prolapse. Three-dimensional reconstruction would permit integration of intracardiac flow patterns in 3 dimensions to study their determinants and significance, for example, how best to evaluate regurgitant jets that adhere to walls and expand asymmetrically in different dimensions.[1,2]

Finally, the extent and contour of vascular plaques and dissections can only be examined in

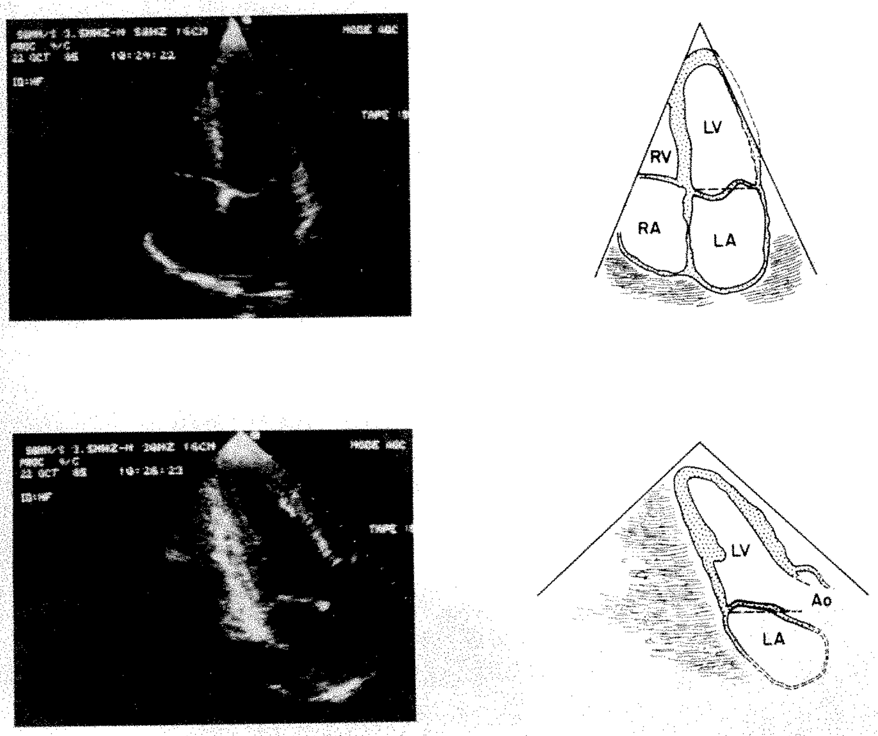

FIGURE 2. Discrepancy of the leaflet–annular relations in roughly orthogonal apical views of an otherwise normal individual. In the mediolateral 4-chamber view (*top*), there is superior displacement of the anterior mitral leaflet beyond a line connecting the annular hinge points, resulting in leaflet concavity toward the apex. In the anteroposterior long-axis view, the leaflets lie entirely on the ventricular side of that line, resulting in an opposite leaflet concavity toward the left atrium (LA). AO = aorta, LV = left ventricle, RA = right atrium, RV = right ventricle.

limited 2-dimensional views by intravascular techniques, whereas 3-dimensional reconstruction could provide the spatial appreciation necessary to guide interventions. The limitations of 2-dimensional echocardiography, therefore, have provided the motivation to develop 3-dimensional techniques.

METHODS

Approaches to 3-dimensional echocardiography: Just as a single ultrasound beam can be scanned through a plane to produce a 2-dimensional sector, it would seem reasonable to take such a sector and scan it, in turn, through space to produce a 3-dimensional acquisition. With existing technology, however, such an acquisition would not allow cardiac motion to be visualized: for example, scanning 30 sectors, each requiring 33 msec for their generation, would require 990 msec, or at least one or more cardiac cycles.

Localization techniques: The advantage of using a best-fit technique to combine multiple intersecting 2-dimensional images using *assumed* locations has been demonstrated by the ability of such an approach to generate a map of endocardial surface area with superimposed regions of wall motion abnormality[3,4]; this map has permitted quantitative studies of the natural history of infarction and the response to reperfusion. In order to reconstruct asymmetries of ventricular shape and nonventricular structures, however, true 3-dimensional localization is required. This can be achieved by 2 kinds of techniques: (1) those restricting the scan to a predetermined *fixed geometry of image acquisition* to simplify the analysis, including the use of parallel planes, tilt or rotation about fixed pivot points, and mechanically rotating scanheads (such as multiplane transesophageal transducers)[5–11]; and (2) techniques allowing *unrestricted scanning*, with 3-dimensional information provided by *spatial locators* (acoustic, electromagnetic, and articulated locator arms) (Figure 1).[12–19]

Limitations of existing approaches: Parallel-slice techniques[5] are most applicable to the open-chest situation, without intervening chest wall structures, whereas fixed-point techniques may not always provide uniformly adequate echocardiographic views or visualize the entire chamber of interest from a single window. Although the feasibility of initial reconstructive approaches has been demonstrated in the research environment,[5–19] their application to larger populations has been restricted by the time-consuming process of coordinating images with their spatial locations. Most techniques slowly acquire individual images and their 3-dimensional locations at discrete, sequential points in time, in order to associate each image with its corresponding location, and these are therefore subject to potential inaccuracies caused by patient motion and respiration between images. Continuous, rapid acquisition of multiple, unrestricted views[19] overcomes these limitations but compounds the problem of coordinating the large numbers of images generated with their corresponding positional data. In previous studies, this proved to be a rate-limiting step, involving multiple computers, manual intervention, and thus prohibitively protracted acquisition times, particularly for dynamic reconstructions at multiple points within the cardiac cycle.[20]

Integrated system for 3-dimensional reconstruction: To overcome these limitations, a *fully integrated system* has recently been developed with the goal of facilitating applications. It automatically integrates images and positional data in real time by interfacing both the 2-dimensional imaging system and the spatial locating device to a single computer, which overlays the positional data in binary format on an unused portion of the imaging signal and records the composite on videotape.[21] This mechanism allows acquisition of spatially registered data during the routine echocardiographic examination, with time and storage requirements no greater than those for the component 2-dimensional scans. A dedicated workstation also includes mechanisms for tracing, dynamic display, and analysis of structures of interest in a 3-dimensional format. The resulting enhanced efficiency of reconstruction has increased applicability to clinical and research problems, some of which will now be reviewed.

APPLICATIONS

Mitral valve prolapse: The need to study mitral leaflet–annular relations in order to refine the diagnosis of mitral valve prolapse has presented a *uniquely 3-dimensional problem* requiring information previously unavailable from the 2-dimensional technique and has therefore provided further impetus to develop the required technology. The original 2-dimensional studies showed that normal mitral leaflets coapt below (on the ventricular side of) a line connecting the annular hinge points in the parasternal long-axis view of the left ventricle, which is oriented anteroposteriorly[22,23]; displacement above this line correlated with angiographic prolapse.[23] Subsequently, however, criteria were extended to include superior leaflet displacement in the mediolateral apical 4-chamber view, which

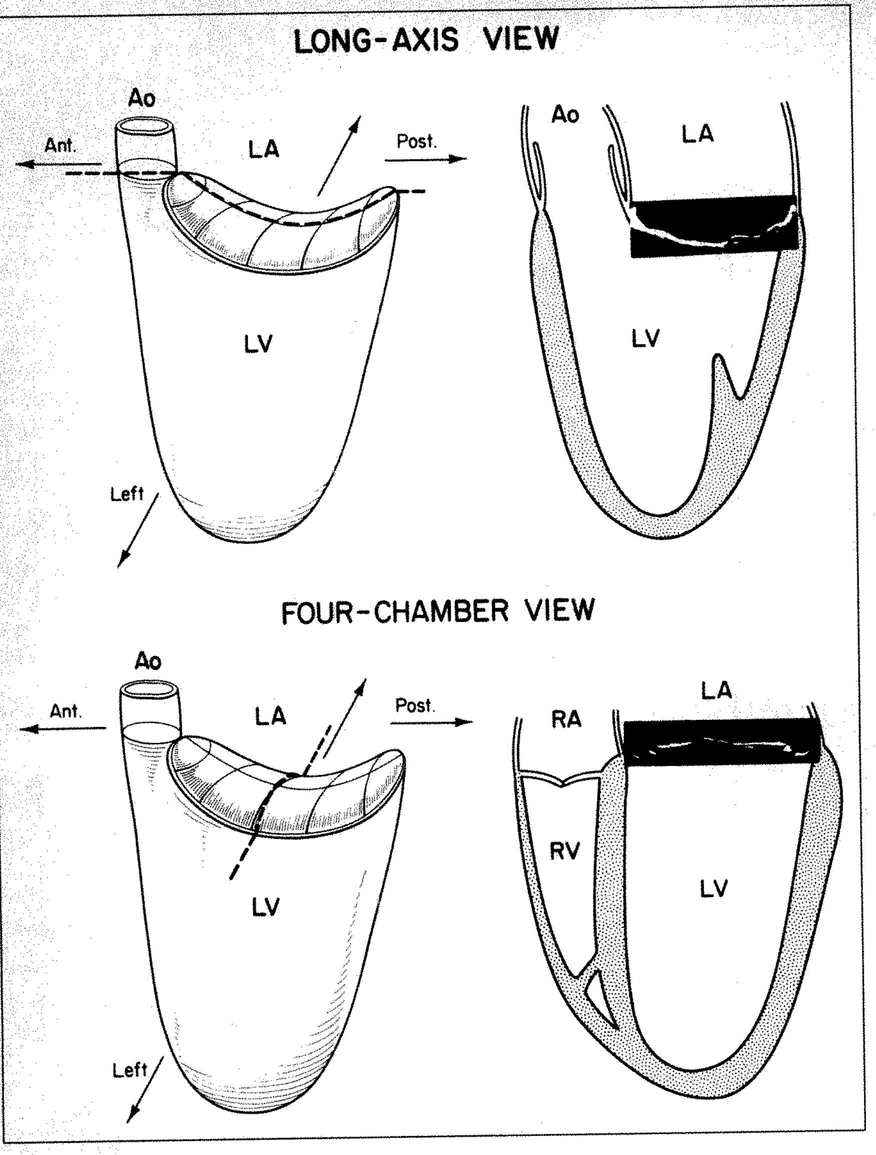

FIGURE 3A: Discrepancy of leaflet–annular relations in echocardiographic views of a model of a saddle-shaped mitral valve imaged in a water bath. The heavy interrupted lines on the left indicate the plane of view. On the right, echocardiographic images are shown along with diagrams of the surrounding structures. The apparent superior displacement in the 4-chamber view simply reflects the overall saddle shape, defined by opposite concavities in roughly perpendicular views.

was rapidly adopted as the diagnostic standard, in part because of its greater yield of positive findings.[24,25] *This extension implied the tacit assumption that the mitral annulus must be a euclidean plane*, so that leaflet displacement could be assessed with equal validity in these intersecting views. The clinical consequences of this technical assumption were profound: by these criteria, prolapse could be diagnosed in 11–13% or more of the general population, including individuals preselected to be normal[26]; moreover, most such individuals had displacement in the 4-chamber view only, not in the long-axis view (Figure 2).

Hypothesis of annular nonplanarity: This frequent discrepancy of leaflet–annular relations in roughly orthogonal views suggested the hypothesis that the appearance of prolapse in such cases reflects a nonplanar 3-dimensional configuration of the mitral apparatus itself, as opposed to any localized leaflet distortion above a planar annulus. Specifically, the observed discrepancy would result if the annulus were saddle-shaped, as shown in Figure 3A, with its high points (farthest from the apex) located anteriorly near the aortic root and posteriorly near the posterior left ventricular wall, and its low points located medially and laterally.[27] The leaflets would, therefore, appear to lie *below* the annular hinge points in a long-axis view through the high points of the annulus and would appear to lie *above* the annular hinge points in a mediolateral 4-chamber view through the low points of the annulus, since the leaflets must span the space between these low and high points. These opposite leaflet–annular relations in perpendicular views, reproducing the discrepant appearances often seen in normal individuals, could be demonstrated in a nonplanar model of the closed mitral valve with a simple saddle-shape annulus and valve (Figure

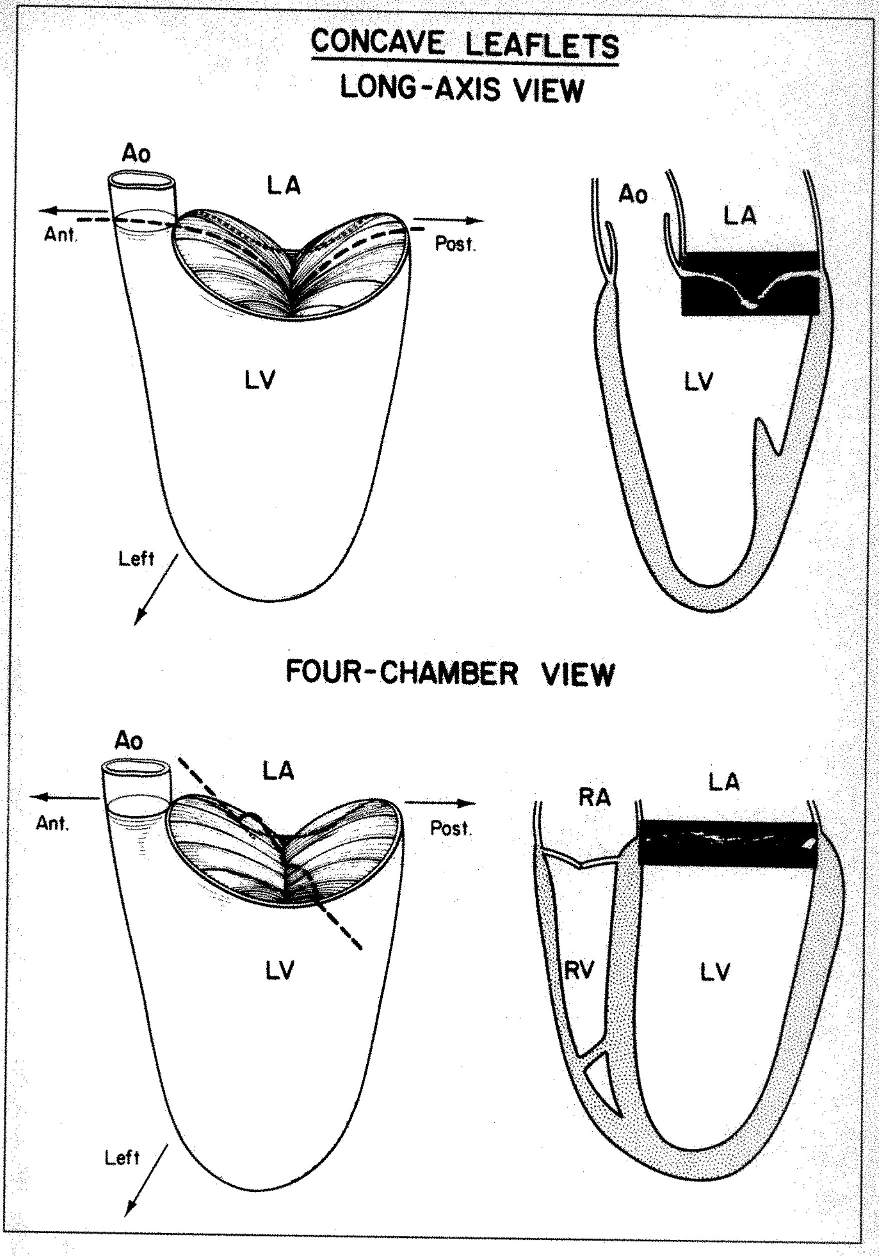

FIGURE 3B: Discrepancy of leaflet–annular relations in echocardiographic views of the model with a saddle-shaped annulus and leaflets that are concave toward the left ventricle, reflecting its distending pressure. Ant. = anterior, AO = aorta, LA = left atrium, LV = left ventricle, Post. = posterior, RA = right atrium, RV = right ventricle. (Reprinted with permission from *Circulation*.[27])

3B). However, while this hypothesis of annular nonplanarity could be *suggested* by 2-dimensional findings in patients and illustrated by the model studies, it could only be proved by 3-dimensional reconstruction of the mitral valve and annulus in vivo.

Three-dimensional reconstruction: The initial approach used to explore the hypothesis of annular nonplanarity used a fixed geometry of acquisition and required no technology other than a standard 2-dimensional transducer and an inclinometer (a fluid-filled cylinder containing an air bubble, allowing rotational views to be obtained in a controlled manner).[28] The mitral annulus was reconstructed in 20 patients from a series of 6 views obtained by rotation about a fixed point at the cardiac apex, revealing a consistent saddle-shaped configuration with anterior and posterior high points (Figure 4),[27] consistent with studies using radio-opaque markers implanted along the canine mitral annulus.[29,30] However, these rotational echocardiographic studies were limited to the mitral annulus and, therefore, could not demonstrate directly the postulated leaflet–annular relations in orthogonal views; moreover, the reconstruction relied on the geometric assumption that the annulus is roughly elliptical, so that maximal diameters at various degrees of rotation would bisect each other at the center of the annulus.[28]

In order to reconstruct the entire mitral valve and annulus without making any geometric assumption, a system was adopted that uses audible sound to locate the transducer[13,15](Figure 1). Three spark gap-locating devices are incorporated into a Plexiglas sleeve rigidly attached to a 2-dimensional transducer. When current is passed through the 2 wires of each locator, a spark crosses the intervening gap, generating an audible sound. An array of microphones times the arrival of this sound and determines the spark gap location by triangulation. The 3 spark gaps are fired in rapid sequence, and each time a full set of 3 positions is known, the position of the transducer can be determined and, from this, the position of the ultrasound image. This technique was modified to permit simultaneous and continuous real-time acquisition of images and positional data by rapidly firing the spark gaps in sequence, following a trigger signal that is recorded by the ultrasound system in order to allow coordination of the imaging and positional data sets.[19]

Results: Reconstructions of the closed mitral valve by this technique in 15 normal subjects scanned in multiple intersecting views reconfirmed annular nonplanarity (Figure 5) and demonstrated the saddle shape of the entire mitral valve. As shown in Figure 6, the leaflet surface (a topographic map created from the intersecting traces) has opposite concavities when viewed in 2 perpendicular perspectives, a characteristic that defines a "saddle" surface. The implications of this shape are illustrated in Figure 7, which shows that the superior leaflet displacement evident in the mediolateral 4-chamber view lies well below the high points of the valve, which can only be appreciated in the long-axis view perspective. Therefore, the apparent displacement in the mediolateral view lies entirely within the bounds defined by the mitral annulus and occurs without leaflet distortion or actual displacement above the entire mitral valve.[19] Therefore, the 3-dimensional technique has been able to explain the clinically observed discrepancy of leaflet–annular relations in perpendicular views, often seen in otherwise normal individuals. This technique has also been used to quantitate the extent of superior leaflet displacement (relative to the average plane of the annulus or its upper margin) in patients in order to distinguish prolapse from a range of normal leaflet positions.[31] Dynamic reconstruction has further been able to display time-varying leaflet–annular relations throughout the cardiac cycle and the normality of annular expansion (in parallel with left atrium expansion) in mid-to-late systole.[20]

Clinical implications and extensions: The results of this 3-dimensional work have allowed us to consider superior systolic displacement isolated to the 4-chamber view within the range of normal

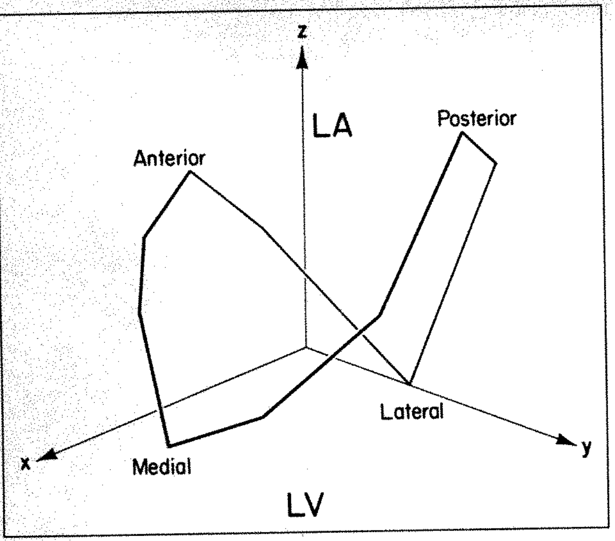

FIGURE 4. Reconstructed mitral annulus in systole in a patient studied with the rotational technique. Abbreviations are as in Figure 3.

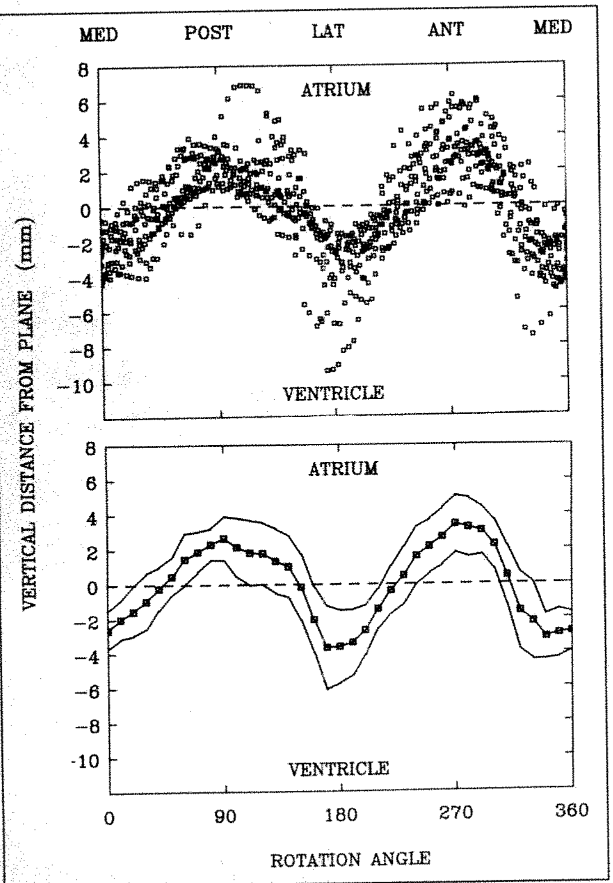

FIGURE 5. Annular nonplanarity: graph of annular height above the reference plane (least-squares plane fitted to the annulus) versus rotational angle around the annular circumference. The zero reference point of rotation was taken as the view demonstrating the long axis of the aortic root most completely. *Upper panel*: pooled data from 15 subjects. *Lower panel*: mean (squares) plus standard deviation. Ant = anterior, Lat = lateral, Post = posterior. (Reprinted with permission from *Circulation*.[19])

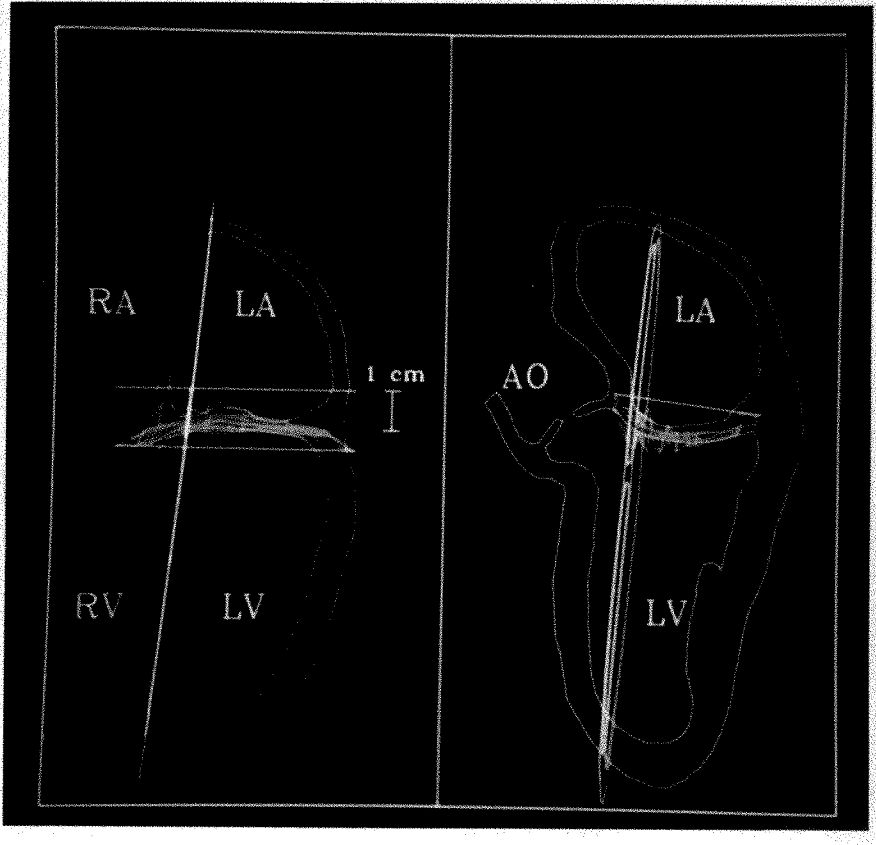

FIGURE 6. Reconstructions of the mitral valve during systole viewed in the perspective of the apical 4-chamber view (*left*) and the long-axis view (*right*). The borders of the cardiac chambers are traced from actual images. Traces of the closed leaflet surface and its annular border are in orange. The straight lines above and below the valve pass through the lowest and highest points of the annulus with respect to the apex, respectively. These views demonstrate that: (1) the leaflet surface has opposite convexities in the 2 perpendicular perspectives, characteristic of a "saddle" surface; and (2) the apparent superior leaflet displacement in the 4-chamber perspective (*left*) lies entirely below the high points of the annulus (upper blue line), which can only be appreciated from the long-axis view. Abbreviations as in Figure 3. (Reprinted with permission from *Circulation*.[19])

leaflet position, consistent with its frequent occurrence in preselected normal subjects.[26] In addition, correlative studies have shown that patients with this finding are similar to those with structurally normal hearts and no displacement in any view: they do not have thickened leaflet or significant mitral regurgitation, the hallmarks of mitral valve prolapse as a disease.[32,33] (It should be noted that these findings apply primarily to the apparent displacement of the anterior leaflet which occurs

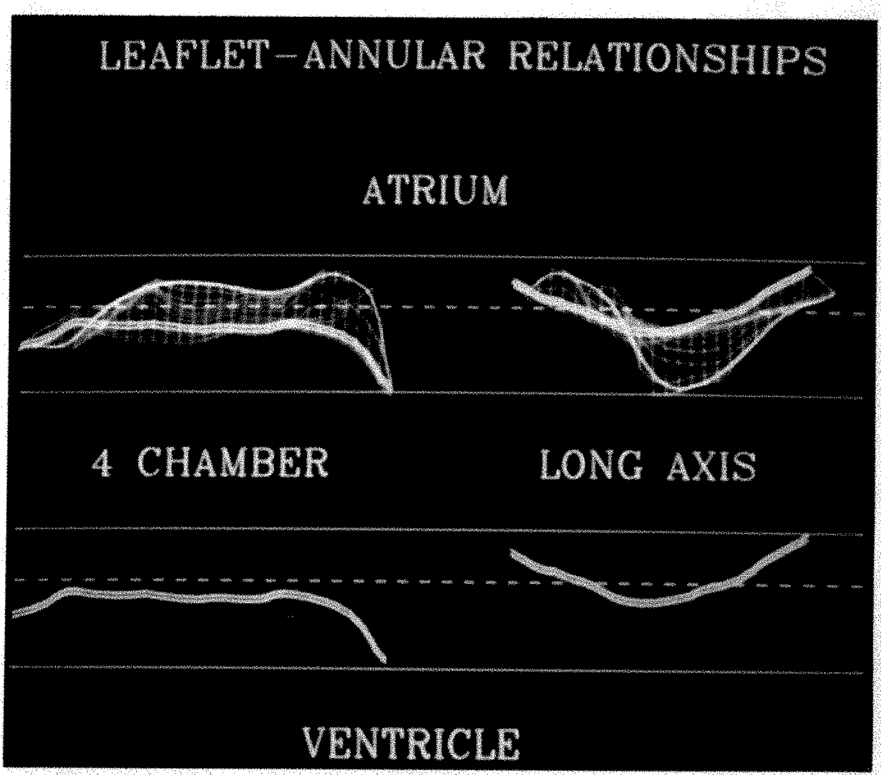

FIGURE 7. *Upper panels*: Reconstructed leaflet surface viewed in 2 perspectives (cf. Figure 6). The double white lines indicate the intersection of this surface with the 4-chamber and long-axis views, giving the traces in the lower panels. The dashed horizontal line represents the plane of least-squares fit to the annular border. Unlike the isolated 2-dimensional images, the 3-dimensional information makes it clear that the superior leaflet displacement evident in the 4-chamber view lies below the high points of the valve. (Reprinted with permission from *Circulation*.[19])

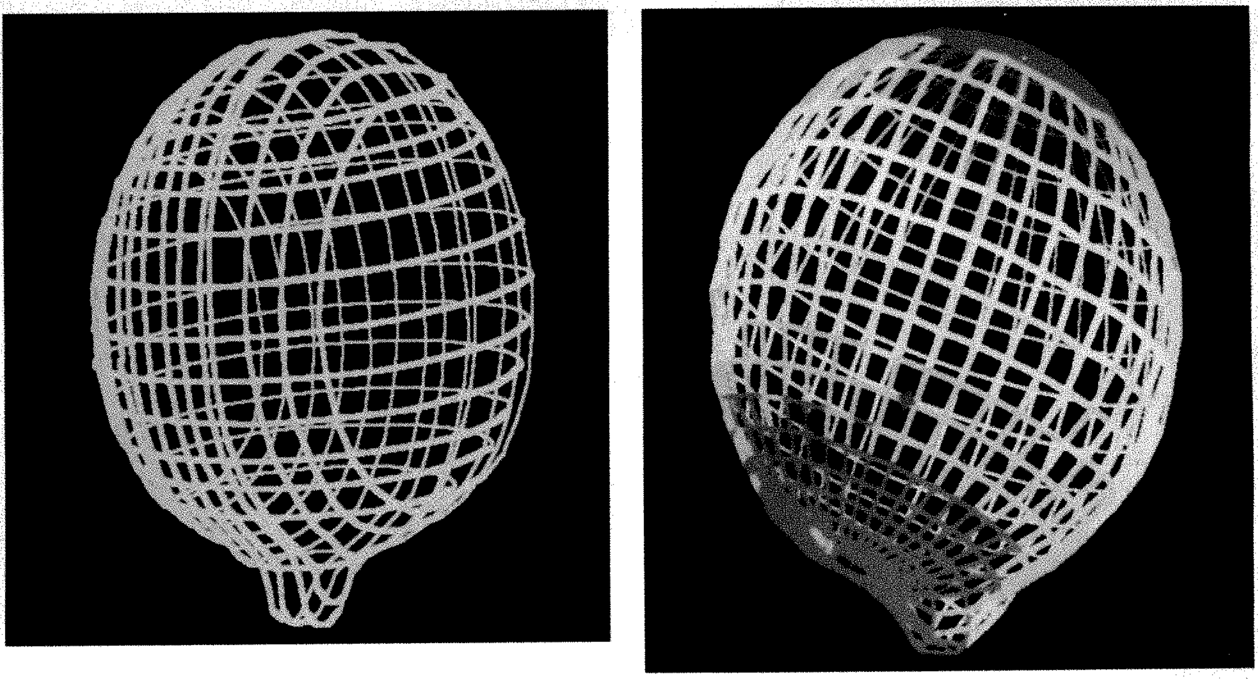

FIGURE 8. Reconstructed traces of a gel-filled ventricular phantom acquired in intersecting views (*A*) with a calculated mathematical surface (*B*).

so frequently in otherwise normal individuals as a consequence of a prominent anterior attachment of that leaflet to the aortic root, which typically constitutes the highest point of the mitral valve. Although prominent, localized prolapse of a posterior leaflet scallop may initially be most evident in the 4-chamber view, it can generally be found by mediolateral scanning of the ultrasound sector in the long-axis orientation as well.[32])

Ventricular volume and contractile function: Although estimates of left ventricular volume, stroke volume, and ejection fraction can be derived by extrapolation from 1- and 2-dimensional data,[34-36] the underlying geometric assumptions often involved are least likely to be applicable when the ventricle is distorted by the effects of ischemic heart disease or right ventricular overload. To provide measures independent of geometric assumptions, the system described herein has been initially applied to reconstruct excised ventricles and ventricular phantoms.[37] It has produced accurate reconstructions over a wide range of shapes and sizes and reproduced localized features, such as papillary muscle indentations and

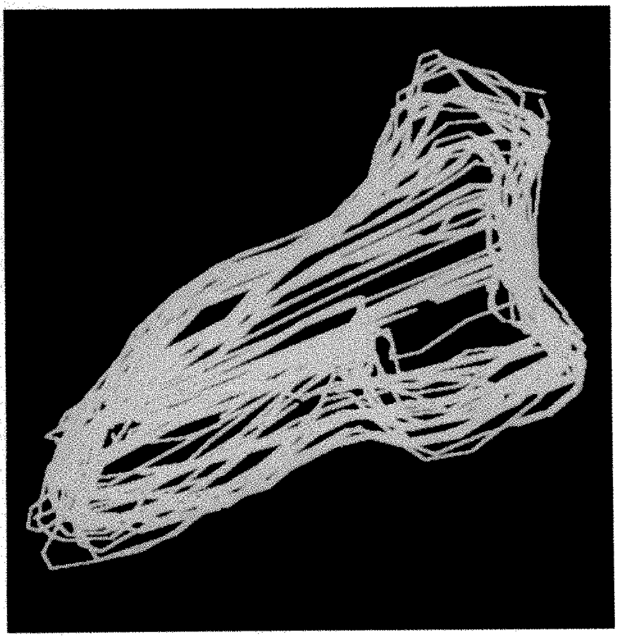

FIGURE 9. Reconstructed endocardial border of a normal human left ventricle with the apex at the left, the outflow tract at the upper right, and a papillary muscle indentation along the inferior surface. (Courtesy of Dr. Jean-Paul Lethor.)

ventricular aneurysms (Figure 8). It can also be applied in patients, as shown in Figure 9. The ability to scan rapidly and continuously, with automated positional data integration, greatly enhances the ease of clinical applicability.

Studies are underway for in vivo validation of these methods in animal models and patients.[38,39] In addition, 3-dimensional echocardiography is being used to improve the accuracy of 2-dimensional plane positioning and derivation of standard measurements such as the left ventricular short-axis diameter by providing real-time 3-dimensional guidance of 2-dimensional scans.[40]

Intravascular ultrasound. By withdrawing a transducer-tipped catheter at known rates through a coronary or peripheral vessel, it is possible to establish the relation of successive 2-dimensional images to one another and reconstruct them in 3-dimensional space. Closely spaced images can provide a gray-scale representation of the vessel wall and lumen in 3-dimensional voxel space, and thresholding programs can then produce a rendering of the intimal surface for convenient viewing.[41] This method also provides longitudinal views of the vessel currently unavailable from the initial 2-dimensional ultrasound images that are only cross-sectional. This method has been applied successfully to facilitate the recognition of dissection and the development of extravascular lumens following angioplasty procedures[41] and is being applied to integrate the thickness of vessel walls and their components.

Transesophageal echocardiography: Transthoracic echocardiography allows transducer position to be varied and determined for 3-dimensional reconstruction, but does not always provide uniform visualization of the cardiac structures from all windows. Systems are therefore being developed for calibrated rotation or translation of transesophageal transducer arrays to permit reconstruction of ventricular and valvular structures in order to answer questions about mitral valve geometry[42] and monitor cardiac function during surgery.[43]

Future directions: By automating the integration of images and spatially locating data, the process of 3-dimensional reconstruction has been considerably expedited. Reconstruction of intravascular images in voxel space, without the need for manual tracing, can now be accomplished in minutes. To streamline quantitative ventricular applications, further work is being done to increase the rate at which multiple images can be acquired and traced. Transducers providing 2 simultaneous orthogonal views[44] or multiple views by phased-array parallel processing[45] should make image acquisition even faster. New systems for on-line border or blood-pool detection (based on signal amplitude or the presence of flow) should facilitate quantitative applications by permitting semiautomation of endocardial border extraction. The availability of a 3-dimensional gray-scale data set[8,11,41] should facilitate border extraction by bridging over and filling in gaps present in individual 2-dimensional views.

Conclusion: Initial studies of 3-dimensional echocardiography have demonstrated its ability to answer uniquely 3-dimensional questions about the shape of the mitral valve and its impact on clinical evaluation. Recent technologic advances are laying the foundation for 3-dimensional echocardiography as the next stage in the evolution of ultrasonic techniques to evaluate the heart, and should allow more routine application of 3-dimensional methods, thereby expanding the range of questions that can be answered. We can anticipate that 3-dimensional echocardiography should be of value in several domains: (1) it can improve our ability to standardize and interpret 2-dimensional scans; (2) it can help us address 3-dimensional questions such as determining complex spatial relations in congenital heart disease[46] and the relation of structural and functional changes in evolution of ischemia and reperfusion; (3) it can allow us to integrate structural information from the echocardiogram with measures of blood flow, metabolism, and tissue characteristics obtained from other 3-dimensional scanning techniques; and (4) it can provide routine noninvasive measures of cardiac chamber size and contractile function. Achieving these goals will depend, in large measure, on our persistence in developing the technologies necessary to facilitate the process of reconstruction and analysis.

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Discussion VI: Three-Dimensional Reconstruction

Dr. Richard Devereaux (New York, New York): We have been working with a slightly different approach to 3-dimensional image reconstruction. My opinion is that the generation of 3-dimensional echo images that do not require the intervening step of tracing and digitizing surfaces will become an important advancement in echo technology. Presently, it is probably best achieved with a system that can scan a plane through a volume. We have used a mechanical sector scanner that rotates within an external housing around a common axis. That is also how the Omniplane system works.

With this system, one probably needs 50–60 cycles, i.e., 50–60 planes, to reconstruct a volume. Over these cycles we can get enough image with further scan conversion to create a volume image. If this is done with high resolution, 512 × 512 pixels, a single cardiac cycle is about 1.25 gigabits of information, which is a tremendous amount. With a work station, however, the processing needed to create the volume image can be done relatively rapidly.

Current and potential problems can actually lead to important insights in how to visualize 3-dimensional information. One relevant consideration is how to see the *z*-axis ("depth") dimension when we are viewing the image. A few high-tech systems have special stereoscopic glasses or incorporate 2 monitors, and these work well. Unfortunately, these are much more expensive than is feasible for standard displays. Therefore, we use alternative approaches, such as lighting the image to cast shadows, using differences in intensity of brightness to portray depth, and rotating the images to take advantage of what is called the "kinetic depth effect" (objects that are closer or farther away move differently and have different angles of motion, depending on their depth relative to the observer.

One of the current problems in echocardiography is that if you do a 3-dimensional image of the heart and then look at it, you see only what the surgeon sees in the operating room, which is the outer surface of the heart—but not the inside. Wire loop diagrams overcome this problem. However, with wire loop diagrams, you also lose all the information about tissue texture and brightness, and this device requires all the intervening steps of digitizing surfaces. I believe we will see many developments in the near future as we find new ways to develop 3-dimensional echocardiographic images that do not require extensive digitization.

Participant: Of all the methods we have worked with, including magnetic resonance imaging (MRI), fast computed tomography (CT) and echocardiography, echocardiography is much harder to work with than any other technique. The kinds of display and analysis software packages that have been developed for other technologies are numerous, extremely development intensive, and enormously advanced relative to anything that has been applied to echocardiography.

All too often in the 3-dimensional display uses, and in cardiac imaging technology in general, we have made excellent images, but without a practical application. There is a major difference between acquiring the necessary data, the 3-dimensional data set, and actually doing the reconstruction and display. One does not need to do the display in order to get volumetric information, for example, in many situations. I believe it is important first to try to identify the application. Probably the only routine surgical operation for which 3-dimensional echocardiography will have a significant use is mitral valve repair. I think that is the initial application in terms of surgical planning.

Second, a data-quality problem surrounds this technology more than any other aspect of ultrasound. This is because if you are trying to register data correctly in 4 dimensions (3-dimensional space plus time), reliable data must be available at the beginning of the procedure. Almost inevitably this means that we have to turn to transesophageal, intravascular, or some other high image-quality technique in order to get adequate data for these kinds of applications.

Third, I believe that whatever the data source is, it is necessary to have the full flexibility of moving the transducer in 3-dimensional space itself in order to get sufficient data to make good reconstructions. That remains a challenge, particularly on the transesophageal window in terms of doing the reconstruction and registration of data, even with biplane or omniplane approaches.

Fourth, displays need to be done quickly—and they can be with other technologies. The echocardiologist who performs 3-dimensional MRI reconstructions at our institution can complete a study, bring the tape to our workstation network, and have a 3-dimensional display running for evaluation within 45 minutes to 1 hour. We need a quick turnaround in order to provide clinical utility. It is essential to be able to do real-time manipulation of the 3-dimensional displays in order to quantitate information in a flexible, operator-selected way. This has become an important issue in designing software packages for use in this area.

Finally, there is a significant problem with practical display techniques. A group from the Mayo Clinic used an oscillating mirror to get a more effective 3-dimensional representation, and several stereovideo techniques were also available, but this still remains a problem.

These are some of the current considerations in the field of 3-dimensional echocardiographic image reconstruction. I believe 3-dimensional is worth pursuing for highly selected applications, but one has to be sure at the onset that the application has clinical utility.

Dr. Alan Pearlman (Seattle, Washington): The principle of taking multiple tomographic images and reregistering them spatially to examine their contours and complex geometry is straightforward, and the technology is now more advanced. Three-dimensional reconstruction is a method that potentially allows us to get extremely accurate information. Several years ago, we conducted in vivo experiments in a dog model that showed instantaneous volume from a volumetric chamber in the solid line, and the actual data points traced frame-by-frame through the cycle. The data are potentially accurate in the in vivo model and have a relatively direct standard of reference. Three-dimensional echocardiography also allows us to get anatomic information in the case of asymmetrical ventricles, which is both a realistic application and an advantage over 2-dimensional echocardiography.

The immediate problems in this technology involve border identification and display issues. I think we get reasonably good images from 2-dimensional echo instruments. The better the images, the easier it is to make determinations. The transducer-locating approach has several potential uses that are both clinically appropriate and functional.

Another major problem we encounter is noisy data. The identification of true contours or borders, as opposed to tissue or blood, remains a challenge. We must make the distinction between a clinically practical and an investigational technique. These are not trivial distinctions. Although there is important information for us to learn about cardiac geometry, dynamics, and function in a 3-dimensional sense, it may or may not translate into a clinically useful tool. Another complicating feature is that, because of the need for experienced observers doing the borders and because of unfamiliarity with complex 3-dimensional displays and data analysis, we often take 3-dimensional data and analyze them in selected 2-dimensional planes. This is a process that somewhat curtails our own research efforts.

We do not have gold standards for most aspects of 3-dimensional scans, and therefore, we must accept at face value that what we have constructed is accurate and does not show registration artifact, motion artifact, or artifact related to noise in the images.

Participant: We began our work in 3-dimensional reconstruction by trying to look at the lower 95% confidence limits. We believed that if we had realistic 3-dimensional geometry from patient to patient, we would be better able to determine if our therapeutic interventions were successful. Needless to say, we should have a sound scientific basis for the interventions and drugs we use. Because the first 3-dimensional reconstructions took 2.5 weeks to accomplish, and since we had to photograph and digitize the copy, it became obvious that this technique was not practical in following patients. When we analyzed the errors, the major problem was in the quality of the borders. Over time, the software packages for 3-dimensional reconstruction have improved and exceeded anything that we could have done in the past in terms of putting 3 dimensions together. However, I believe that the problems with border quality will be difficult to overcome and I do not see any potential solutions in the near future.

I agree with other panelists that the subjects of quantitation and quantitation refinement (to the point that we can make decisions on the variability of patients and the efficacy of our therapies) are probably the most important single issues in the field of echocardiography today.

Dr. Donald King (Darien, Connecticut): We are still in the very early stages of developing 3-dimensional echocardiography, and it is important to note the different directions that various researchers have taken. Dr. Weyman's work is obviously sophisticated and has exotic images but, perhaps because of budget limitations, we have gone in the opposite direction and tried to use 3-dimensional imaging in the context of our current work to improve 2-dimensional examination, to increase accuracy and cost effectiveness, and basically to add value by improving quantitation. We can quantitate now, but in the future we want to get hard data and then add what 3-dimensional scans can uniquely contribute.

Our system is basically clinical. Obviously we are also using it for research, but it has been designed to be integrated into a clinical system that currently exists for virtually any echocardiography machine, and we can then add on our 3-dimensional spatial locater. It is a spark-gap system based on the concept that Dr. Weyman described. However, this is an interactive on-line system that operates in the same way as the 2-dimensional examination. We use the 3-dimensional spatial data immediately to affect the course of the examination. We also use the 3-dimensional system to provide us with a method for visual guidance for positioning 2-dimensional images with regard to their orthogonal, or nonvisualized, dimension. There is a "line of intersection" display, which involves the operator first taking an image that will be orthogonal to subsequent images, and this line is updated continuously.

We can also use the line of intersection display to control and standardize the positioning of apical views. I believe that this will be a useful application for standardizing and documenting image position. Further, we have used this procedure to test our ability to measure left atrial and left ventricular dimensions. We tested pairs of operators by first doing 2-dimensional and then 3-dimensional scans. Then we measured these dimensions. After comparing the measurements in the comparable planes, we found that by using 3-dimensional imaging we obtained an approximately 3-fold improvement in reproducibility. Obviously, 3-dimensional imaging does improve quantitation of data.

There is no gold standard for accurate, reliable measurements, but we found that our mean dimensions for the left ventricular measurement by 3-dimensional scanning were greater than the 2-dimensional scan dimensions made in the long axis view and in less than the comparable 2-dimensional scan dimensions made in the short-axis view. Clearly, we are honing into a more correct position and obtaining more accurate measurements.

A unique application that we can do with 3-dimensional scanning is guidance of the 2-dimensional examination, which improves accuracy, reproducibility, and documentation of image position. Also, volume computation without geometric assumptions, total endocardial and infarct surface area, and 3-dimensional Doppler are other applications with 3-dimensional imaging. With 3-dimensional Doppler, we can actually measure the Doppler angle, but this application is still experimental. Finally, is the general application of computer graphics—including voxel imaging, surface rendering, and rotation reslicing. We still have not yet developed these parameters.

We could do more complex computer graphics if the hardware were available. Perhaps in the future we will. Presently, we have a simple modeling program, but we are striving to add this program to our clinical system and to use it to enhance the quality and value of the data that we currently generate with the 2-dimensional system. Primarily, I view 3-dimensional scanning as an adjunct or add-on instrument to improve the quality of the 2-dimensional examination.

Dr. Feigenbaum: I think 3-dimensional scanning is an asset now, and the system, when compared with other instruments, is an adjunct to our 2-dimensional machines. Also, the cost is not incrementally prohibitive.

Dr. Arthur Weyman (Boston, Massachusetts): I would like to comment on the surgical planning aspects of 3-dimensional echocardiography. First, it is possible to use CT and do all of the image segmentation entirely on a thresholding basis, without operator intervention. If the data are reliable, then many possible sophisticated applications can be used to look at the effects of a perturbation. Three-dimensional echocardiography has been an extremely effective tool in that area.

In terms of how we apply our primary data for use in ultrasound, we are at the other end of the spectrum. Competing technologies are available, so we should be selective in choosing our applications. As I see it, it will not be practical for 3-dimensional echocardiography to compete with MRI in surgical planning for complex congenital heart disease. On the other hand, there are no technologies competing with echocardiography for valvular reconstruction, and I believe this is an area where, given the frequency with which the operation is now being performed, 3-dimensional echocardiography could have an enormous practical impact.

Dr. Julius Gardin (Orange, California): Dr. Devereaux, regarding your approach, does it depend on scanning from an apex or fanning out from a fixed point? Perhaps you could expand on how those sections are obtained.

Dr. Devereaux: It depends on having a window where you can image well and also on holding the transducer stable for enough cardiac cycles to acquire an image. For an electronic system, it would require 50–60 cycles and <1 minute. The way we do it is to come back to the 180° image: 3 images are done at 1 time, and the 61st image should be a mirror image of the first. If it is a mirror image, then you have done well in holding the transducer position stable.

Our system, which includes a very small add-on computer that is hooked into the machine, indicates the degrees of rotation on each frame from start to zero and then proceeds to 180°. We can put 2 triggers in per frame, so we can do it in diastole, systole, some other point, or simply indicate the start at end-diastole.

Dr. Weyman: One of the major advantages of 3-dimensional data acquisition is that it eliminates many of the image quality problems. When you try to make reconstructions from 2-dimensional images, you have to define a coherent surface or define the whole outline of the ventricle. However, with 3-dimensional reconstruction, it is possible to take a little piece of the wall that is well perceived and add 1 or 2 pieces to build up a complete model, without having to see the entire image clearly in any particular plane. It is amazing how much it facilitates the quantitative measurement and how broadly it expands the number of subjects that can be studied.

The process is similar to the difference between segmental systems and quantitative systems. Echocardiographers prefer segmental analysis of wall motion because you may see a segment in 1 of 10 different views and not anywhere else. You can then take the little pieces out and put them together, rather than try to get the whole outline in one projection.

Participant: In order to do 3-dimensional reconstruction accurately, you have to deal with respiratory motion, which is a major problem, as is obtaining a spatially correct data set acquisition.

Comparing the accuracy of volumetric variables is not a rigorous test of this kind of work. It is more important to validate a shape, which is a much more complicated procedure in terms of the analytic strategies that are appropriate for its use. I have not seen any work with 3-dimensional cardiac image reconstruction that has advanced in this direction. Research along these lines would have relevant applications in clinical use.